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(54) Title: HUMAN TRANSMEMBRANE PROTEINS

(57) Abstract

The invention provides human transmembrane proteins (HTMPN) and polynucleotides which identify and encode HTMPN. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of HTMPN.

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HUMAN TRANSMEMBRANE PROTEINS

TECHNICAL FIELD

This invention relates to nucleic acid and amino acid sequences of human transmembrane proteins and to the use of these sequences in the diagnosis, treatment, and prevention of immune, reproductive, smooth muscle, neurological, gastrointestinal, developmental, and cell proliferative disorders.

BACKGROUND OF THE INVENTION

Eukaryotic organisms are distinct from prokaryotes in possessing many intracellular organelle and vesicle structures. Many of the metabolic reactions which distinguish eukaryotic biochemistry from prokaryotic biochemistry take place within these structures. In particular, many cellular functions require very stringent reaction conditions, and the organelles and vesicles enable compartmentalization and isolation of reactions which might otherwise disrupt cytosolic metabolic processes. The organelles include mitochondria, smooth and rough endoplasmic reticula, sarcoplasmic reticulum, and the Golgi body. The vesicles include phagosomes, lysosomes, endosomes, peroxisomes, and secretory vesicles. Organelles and vesicles are bounded by single or double membranes.

Biological membranes are highly selective permeable barriers made up of lipid bilayer sheets composed of phosphoglycerides, fatty acids, cholesterol, phospholipids, glycolipids, proteoglycans, and proteins. Membranes contain ion pumps, ion channels, and specific receptors for external stimuli which transmit biochemical signals across the membranes. These membranes also contain second messenger proteins which interact with these pumps, channels, and receptors to amplify and regulate transmission of these signals.

Plasma Membrane Proteins

Plasma membrane proteins (MPs) are divided into two groups based upon methods of protein extraction from the membrane. Extrinsic or peripheral membrane proteins can be released using extremes of ionic strength or pH, urea, or other disruptors of protein interactions. Intrinsic or integral membrane proteins are released only when the lipid

bilayer of the membrane is dissolved by detergent.

Transmembrane proteins (TM) are characterized by an extracellular, a transmembrane, and an intracellular domain. TM domains are typically comprised of 15 to 25 hydrophobic amino acids which are predicted to adopt an α-helical conformation. TM proteins are classified as bitopic (Types I and II) proteins, which span the membrane once, and polytopic (Types III and IV) (Singer, S.J. (1990) Annu. Rev. Cell Biol. 6:247-96) proteins which contain multiple membrane-spanning segments. TM proteins that act as cell-surface receptor proteins involved in signal transduction include growth and differentiation factor receptors, and receptor-interacting proteins such as *Drosophila* pecanex and frizzled proteins, LIV-1 protein, NF2 protein, and GNS1/SUR4 eukaryotic integral membrane proteins. TM proteins also act as transporters of ions or metabolites, such as gap junction channels (connexins), and ion channels, and as cell anchoring proteins, such as lectins, integrins, and fibronectins. TM proteins are found in vesicle organelle-forming molecules, such as calveolins; or cell recognition molecules, such as cluster of differentiation (CD) antigens, glycoproteins, and mucins.

Many membrane proteins (MPs) contain amino acid sequence motifs that serve to localize proteins to specific subcellular sites. Examples of these motifs include PDZ domains, KDEL, RGD, NGR, and GSL sequence motifs, von Willebrand factor A (vWFA) domains, and EGF-like domains. RGD, NGR, and GSL motif-containing peptides have been used as drug delivery agents in targeted cancer treatment of tumor vasculature (Arap, W. et al. (1998) Science, 279:377-380). Membrane proteins may also contain amino acid sequence motifs that serve to interact with extracellular or intracellular molecules, such as carbohydrate recognition domains.

Chemical modification of amino acid residue side chains alters the manner in which MPs interact with other molecules, for example, phospholipid membranes. Examples of such chemical modifications to amino acid residue side chains are covalent bond formation with glycosaminoglycans, oligosaccharides, phospholipids, acetyl and palmitoyl moieties, ADP-ribose, phosphate, and sulphate groups.

RNA-encoding membrane proteins may have alternative splice sites which give rise to proteins encoded by the same gene but with different messenger RNA and amino acid sequences. Splice variant membrane proteins may interact with other ligand and protein isoforms.

G-Protein Coupled Receptors

G-protein coupled receptors (GPCR) are a superfamily of integral membrane proteins which transduce extracellular signals. GPCRs include receptors for biogenic amines, lipid mediators of inflammation, peptide hormones, and sensory signal mediators. The structure of these highly-conserved receptors consists of seven hydrophobic transmembrane (serpentine) regions, cysteine disulfide bridges between the second and third extracellular loops, an extracellular N-terminus, and a cytoplasmic C-terminus. Three extracellular loops alternate with three intracellular loops to link the seven transmembrane regions. The most conserved parts of these proteins are the transmembrane regions and the first two cytoplasmic loops. A conserved, acidic-Arg-aromatic residue triplet present in the second cytoplasmic loop may interact with G proteins. A GPCR consensus pattern is characteristic of most proteins belonging to this superfamily (ExPASy PROSITE document PS00237; and Watson, S. and S. Arkinstall (1994) The G-protein Linked Receptor Facts Book, Academic Press, San Diego, CA, pp 2-6). Mutations and changes in transcriptional activation of GPCR-encoding genes have been associated with neurological disorders such as schizophrenia, Parkinson's disease, Alzheimer's disease, drug addiction, and feeding disorders.

Scavenger Receptors

Macrophage scavenger receptors with broad ligand specificity may participate in the binding of low density lipoproteins (LDL) and foreign antigens. Scavenger receptors types I and II are trimeric membrane proteins with each subunit containing a small N-terminal intracellular domain, a transmembrane domain, a large extracellular domain, and a C-terminal cysteine-rich domain. The extracellular domain contains a short spacer domain, an α-helical coiled-coil domain, and a triple helical collagenous domain. These receptors have been shown to bind a spectrum of ligands, including chemically modified lipoproteins and albumin, polyribonucleotides, polysaccharides, phospholipids, and asbestos (Matsumoto, A. et al. (1990) Proc. Natl. Acad. Sci. 87:9133-9137; and Elomaa, O. et al. (1995) Cell 80:603-609). The scavenger receptors are thought to play a key role in atherogenesis by mediating uptake of modified LDL in arterial walls, and in host defense by binding bacterial endotoxins, bacteria, and protozoa.

Tetraspan family proteins

The transmembrane 4 superfamily (TM4SF) or tetraspan family is a multigene

family encoding type III integral membrane proteins (Wright, M.D. and Tomlinson, M.G. (1994) Immunol. Today 15:588). TM4SF is comprised of membrane proteins which traverse the cell membrane four times. Members of the TM4SF include platelet and endothelial cell membrane proteins, melanoma-associated antigens, leukocyte surface glycoproteins, colonal carcinoma antigens, tumor-associated antigens, and surface proteins of the schistosome parasites (Jankowski, S.A. (1994) Oncogene 9:1205-1211). Members of the TM4SF share about 25-30% amino acid sequence identity with one another.

A number of TM4SF members have been implicated in signal transduction, control of cell adhesion, regulation of cell growth and proliferation, including development and oncogenesis, and cell motility, including tumor cell metastasis. Expression of TM4SF proteins is associated with a variety of tumors and the level of expression may be altered when cells are growing or activated.

Tumor Antigens

Tumor antigens are surface molecules that are differentially expressed in tumor cells relative to normal cells. Tumor antigens distinguish tumor cells immunologically from normal cells and provide diagnostic and therapeutic targets for human cancers (Takagi, S. et al. (1995) Int. J. Cancer 61: 706-715; Liu, E. et al. (1992) Oncogene 7: 1027-1032).

Ion channels

Ion channels are found in the plasma membranes of virtually every cell in the body. For example, chloride channels mediate a variety of cellular functions including regulation of membrane potentials and absorption and secretion of ions across epithelial membranes. When present in intracellular membranes of the Golgi apparatus and endocytic vesicles, chloride channels also regulate organelle pH (see, e.g., Greger, R. (1988) Annu. Rev. Physiol. 50:111-122). Electrophysiological and pharmacological properties of chloride channels, including ion conductance, current-voltage relationships, and sensitivity to modulators, suggest that different chloride channels exist in muscles, neurons, fibroblasts, epithelial cells, and lymphocytes.

Many channels have sites for phosphorylation by one or more protein kinases including protein kinase A, protein kinase C, tyrosine kinase, and casein kinase II, all of which regulate ion channel activity in cells. Inappropriate phosphorylation of proteins in cells has been linked to changes in cell cycle progression and cell differentiation. Changes

in the cell cycle have been linked to induction of apoptosis or cancer. Changes in cell differentiation have been linked to diseases and disorders of the reproductive system, immune system, and skeletal muscle.

Proton pumps

Proton ATPases are a large class of membrane proteins that use the energy of ATP hydrolysis to generate an electrochemical proton gradient across a membrane. The resultant gradient may be used to transport other ions across the membrane (Na^+, K^+, or Cl^-) or to maintain organelle pH. Proton ATPases are further subdivided into the mitochondrial F-ATPases, the plasma membrane ATPases, and the vacuolar ATPases. The vacuolar ATPases establish and maintain an acidic pH within various vesicles involved in the processes of endocytosis and exocytosis (Mellman, I. et al. (1986) Ann. Rev. Biochem. 55:663-700).

Proton-coupled, 12 membrane-spanning domain transporters such as PEPT 1 and PEPT 2 are responsible for gastrointestinal absorption and for renal reabsorbtion of peptides using an electrochemical H^+ gradient as the driving force. Another type of peptide transporter, the TAP transporter, is a heterodimer consisting of TAP 1 and TAP 2 and is associated with antigen processing. Peptide antigens are transported across the membrane of the endoplasmic reticulum by TAP so they can be expressed on the cell surface in association with MHC molecules. Each TAP protein consists of multiple hydrophobic membrane spanning segments and a highly conserved ATP-binding cassette (Boll, M. et al. (1996) Proc. Natl. Acad. Sci. 93:284-289). Pathogenic microorganisms, such as herpes simplex virus, may encode inhibitors of TAP-mediated peptide transport in order to evade immune surveillance (Marusina, K. and Manaco, J.J. (1996) Curr. Opin. Hematol. 3:19-26).

ABC Transporters

The ATP-binding cassette (ABC) transporters, also called the "traffic ATPases", comprise a superfamily of membrane proteins that mediate transport and channel functions in prokaryotes and eukaryotes (Higgins, C.F. (1992) Annu. Rev. Cell Biol. 8:67-113). ABC proteins share a similar overall structure and significant sequence homology. All ABC proteins contain a conserved domain of approximately two hundred amino acid residues which includes one or more nucleotide binding domains. Mutations in ABC transporter genes are associated with various disorders, such as hyperbilirubinemia

II/Dubin-Johnson syndrome, recessive Stargardt's disease, X-linked adrenoluekodystrophy, multidrug resistance, celiac disease, and cystic fibrosis.

Membrane Proteins Associated with Intercellular Communication

Intercellular communication is essential for the development and survival of multicellular organisms. Cells communicate with one another through the secretion and uptake of protein signaling molecules. The uptake of proteins into the cell is achieved by endocytosis, in which the interaction of signaling molecules with the plasma membrane surface, often via binding to specific receptors, results in the formation of plasma membrane-derived vesicles that enclose and transport the molecules into the cytosol. The secretion of proteins from the cell is achieved by exocytosis, in which molecules inside of the cell are packaged into membrane-bound transport vesicles derived from the *trans*-Golgi network. These vesicles fuse with the plasma membrane and release their contents into the surrounding extracellular space. Endocytosis and exocytosis result in the removal and addition of plasma membrane components and the recycling of these components is essential to maintain the integrity, identity, and functionality of both the plasma membrane and internal membrane-bound compartments.

Lysosomes are the site of degradation of intracellular material during autophagy and of extracellular molecules following endocytosis. Lysosomal enzymes are packaged into vesicles which bud from the *trans*-Golgi network. These vesicles fuse with endosomes to form the mature lysosome in which hydrolytic digestion of endocytosed material occurs. Lysosomes can fuse with autophagosomes to form a unique compartment in which the degradation of organelles and other intracellular components occurs. Protein sorting by transport vesicles, such as the endosome, has important consequences for a variety of physiological processes including cell surface growth, the biogenesis of distinct intracellular organelles, endocytosis, and the controlled secretion of hormones and neurotransmitters (Rothman, J.E. and Wieland, F.T. (1996) Science 272:227-234). In particular, neurodegenerative disorders and other neuronal pathologies are associated with biochemical flaws during endosomal protein sorting or endosomal biogenesis (Mayer R.J. et al. (1996) Adv. Exp. Med. Biol. 389:261-269).

Peroxisomes are organelles independent from the secretory pathway. They are the site of many peroxide-generating oxidative reactions in the cell. Peroxisomes are unique among eukaryotic organelles in that their size, number, and enzyme content vary

depending upon organism, cell type, and metabolic needs. The majority of peroxisome-associated proteins are membrane-bound or are found proximal to the cytosolic or the lumenal side of the peroxisome membrane (Waterham, H.R. and Cregg, J.M. (1997) BioEssays 19:57-66).

Genetic defects in peroxisome proteins which result in peroxisomal deficiencies have been linked to a number of human pathologies, including Zellweger syndrome, rhizomelic chonrodysplasia punctata, X-linked adrenoleukodystrophy, acyl-CoA oxidase deficiency, bifunctional enzyme deficiency, classical Refsum's disease, DHAP alkyl transferase deficiency, and acatalasemia (Moser, H.W. and Moser, A.B. (1996) Ann. NY Acad. Sci. 804:427-441). In addition, Gartner, J. et al. (1991; Pediatr. Res. 29:141-146) found a 22 kDa integral membrane protein associated with lower density peroxisome-like subcellular fractions in patients with Zellweger syndrome.

Normal embryonic development and control of germ cell maturation is modulated by a number of secretory proteins which interact with their respective membrane-bound receptors. Cell fate during embryonic development is determined by members of the activin/TGF-β superfamily, cadherins, IGF-2, and other morphogens. In addition, proliferation, maturation, and redifferentiation of germ cell and reproductive tissues are regulated, for example, by IGF-2, inhibins, activins, and follistatins (Petraglia, F. (1997) Placenta 18:3-8; Mather, J.P. et al. (1997) Proc. Soc. Exp. Biol. Med. 215:209-222).

Endoplasmic Reticulum Membrane Proteins

The normal functioning of the eukaryotic cell requires that all newly synthesized proteins be correctly folded, modified, and delivered to specific intra- and extracellular sites. Newly synthesized membrane and secretory proteins enter a cellular sorting and distribution network during or immediately after synthesis and are routed to specific locations inside and outside of the cell. The initial compartment in this process is the endoplasmic reticulum (ER) where proteins undergo modifications such as glycosylation, disulfide bond formation, and assembly into oligomers. The modified proteins are then transported through a series of membrane-bound compartments which include the various cisternae of the Golgi complex, where further carbohydrate modifications occur. Transport between compartments occurs by means of vesicles that bud and fuse in a manner specific to the type of protein being transported. Once within the secretory pathway, proteins do not have to cross a membrane to reach the cell surface.

Although the majority of proteins processed through the ER are transported out of the organelle, some are retained. The signal for retention in the ER in mammalian cells consists of the tetrapeptide sequence, KDEL, located at the carboxyl terminus of proteins (Munro, S. (1986) Cell 46:291-300). Proteins containing this sequence leave the ER but are quickly retrieved from the early Golgi cisternae and returned to the ER, while proteins lacking this signal continue through the secretory pathway.

Disruptions in the cellular secretory pathway have been implicated in several human diseases. In familial hypercholesterolemia the low density lipoprotein receptors remain in the ER, rather than moving to the cell surface (Pathak, R.K. (1988) J. Cell Biol. 106:1831-1841). Altered transport and processing of the β-amyloid precursor protein (βAPP) involves the putative vesicle transport protein presenilin, and may play a role in early-onset Alzheimer's disease (Levy-Lahad, E. et al. (1995) Science 269:973-977). Changes in ER-derived calcium homeostasis have been associated with diseases such as cardiomyopathy, cardiac hypertrophy, myotonic dystrophy, Brody disease, Smith-McCort dysplasia, and diabetes mellitus.

Mitochondrial Membrane Proteins

The mitochondrial electron transport (or respiratory) chain is a series of three enzyme complexes in the mitochondrial membrane that is responsible for the transport of electrons from NADH to oxygen and the coupling of this oxidation to the synthesis of ATP (oxidative phosphorylation). ATP then provides the primary source of energy for driving the many energy-requiring reactions of a cell.

Most of the protein components of the mitochondrial respiratory chain are the products of nuclear encoded genes that are imported into the mitochondria and the remainder are products of mitochondrial genes. Defects and altered expression of enzymes in the respiratory chain are associated with a variety of disease conditions in man, including, for example, neurodegenerative diseases, myopathies, and cancer.

Lymphocyte and Leukocyte Membrane Proteins

The B-cell response to antigens, which is modulated through receptors, is an essential component of the normal immune system. Mature B cells recognize foreign antigens through B cell receptors (BCR) which are membrane-bound, specific antibodies that bind foreign antigens. The antigen/receptor complex is internalized and the antigen is proteolytically processed. To generate an efficient response to complex antigens, the

BCR, BCR-associated proteins, and T cell response are all required. Proteolytic fragments of the antigen are complexed with major histocompatability complex-II (MHCII) molecules on the surface of the B cells where the complex can be recognized by T cells. In contrast, macrophages and other lymphoid cells present antigens in association with MHCI molecules to T cells. T cells recognize and are activated by the MHCI-antigen complex through interactions with the T cell receptor/CD3 complex, a T cell-surface multimeric protein located in the plasma membrane. T cells activated by antigen presentation secrete a variety of lymphokines that induce B cell maturation and T cell proliferation and activate macrophages, which kill target cells.

Leukocytes have a fundamental role in the inflammatory and immune response and include monocytes/macrophages, mast cells, polymorphonucleoleukocytes, natural killer cells, neutrophils, eosinophils, basophils, and myeloid precursors. Leukocyte membrane proteins include members of the CD antigens, N-CAM, I-CAM, human leukocyte antigen (HLA) class I and HLA class II gene products, immunoglobulins, immunoglobulin receptors, complement, complement receptors, interferons, interferon receptors, interleukin receptors, and chemokine receptors.

Abnormal lymphocyte and leukocyte activity has been associated with acute disorders, such as AIDS, immune hypersensitivity, leukemias, leukopenia, systemic lupus, granulomatous disease, and eosinophilia.

Apoptosis-Associated Membrane Proteins

A variety of ligands, receptors, enzymes, tumor suppressors, viral gene products, pharmacological agents, and inorganic ions have important positive or negative roles in regulating and implementing the apoptotic destruction of a cell. Although some specific components of the apoptotic pathway have been identified and characterized, many interactions between the proteins involved are undefined, leaving major aspects of the pathway unknown.

A requirement for calcium in apoptosis was previously suggested by studies showing the involvement of calcium levels in DNA cleavage and Fas-mediated cell death (Hewish, D.R. and L.A. Burgoyne (1973) Biochem. Biophys. Res. Comm. 52:504-510; Vignaux, F. et al. (1995) J. Exp. Med. 181:781-786; Oshimi, Y. and S. Miyazaki (1995) J. Immunol. 154:599-609). Other studies show that intracellular calcium concentrations increase when apoptosis is triggered in thymocytes by either T cell receptor cross-linking

or by glucocorticoids and cell death can be prevented by blocking this increase (McConkey, D.J. et al. (1989) J. Immunol. 143:1801-1806; McConkey, D.J. et al. (1989) Arch. Biochem. Biophys. 269:365-370). Therefore, membrane proteins such as calcium channels are important for the apopoptic response.

Tumorgenesis

Tumorgenesis is associated with the activation of oncogenes which are derived from normal cellular genes. These oncogenes encode oncoproteins which are capable of converting normal cells into malignant cells. Some oncoproteins are mutant isoforms of the normal protein and other oncoproteins are abnormally expressed with respect to location or level of expression. The latter category of oncoprotein causes cancer by altering transcriptional control of cell proliferation. Five classes of oncoproteins are known to affect the cell cycle controls. These classes include growth factors, growth factor receptors, intracellular signal transducers, nuclear transcription factors, and cell-cycle control proteins. These proteins include those which are modified by glycosylation, phosphorylation, glycosaminoglycan attachment, sulphation, and lipidation.

Modulation of factors which act in the coordination of the human cell division cycle may provide an important means to reduce tumorgenesis. An example of the metastasis-associated proteins is the lysosomal membrane glycoprotein P2B/LAMP-1 which is also expressed in normal tissues. (Heffernan, M. et al. (1989) Cancer Res. 49:6077-6084.) In addition, mammalian proteins homologous to the plant pathogenesis-related proteins have been identified in hyperplastic glioma. (Murphy, E.V. et al. (1995) Gene 159:131-135.)

The discovery of new human transmembrane proteins and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of immune, reproductive, smooth muscle, neurological, gastrointestinal, developmental, and cell proliferative disorders.

SUMMARY OF THE INVENTION

The invention features substantially purified polypeptides, human transmembrane proteins, referred to collectively as "HTMPN" and individually as "HTMPN-1", "HTMPN-2", "HTMPN-3", "HTMPN-4", "HTMPN-5", "HTMPN-6", "HTMPN-7", "HTMPN-8", "HTMPN-9", "HTMPN-10", "HTMPN-11", "HTMPN-12", "HTMPN-13",

"HTMPN-14", "HTMPN-15", "HTMPN-16", "HTMPN-17", "HTMPN-18", "HTMPN-19", "HTMPN-20", "HTMPN-21", "HTMPN-22", "HTMPN-23", "HTMPN-24", "HTMPN-25", "HTMPN-26", "HTMPN-27", "HTMPN-28", "HTMPN-29", "HTMPN-30", "HTMPN-31", "HTMPN-32", "HTMPN-33", "HTMPN-34", "HTMPN-35", "HTMPN-36", "HTMPN-37", "HTMPN-38", "HTMPN-39", "HTMPN-40", "HTMPN-41", "HTMPN-42", "HTMPN-43", "HTMPN-44", "HTMPN-45", "HTMPN-46", "HTMPN-47", "HTMPN-48", "HTMPN-49", "HTMPN-50", "HTMPN-51", "HTMPN-52", "HTMPN-53", "HTMPN-54", "HTMPN-55", "HTMPN-56", "HTMPN-57", "HTMPN-58", "HTMPN-59", "HTMPN-60", "HTMPN-61", "HTMPN-62", "HTMPN-63", "HTMPN-64", "HTMPN-65", "HTMPN-66", "HTMPN-67", "HTMPN-68", "HTMPN-69", "HTMPN-70", "HTMPN-71", "HTMPN-72", "HTMPN-73", "HTMPN-74", "HTMPN-75", "HTMPN-76", "HTMPN-77", "HTMPN-78", and "HTMPN-79". In one aspect, the invention provides a substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, and SEQ ID NO:79 (SEQ ID NO:1-79), and fragments thereof.

The invention further provides a substantially purified variant having at least 90% amino acid identity to at least one of the amino acid sequences selected from the group consisting of SEQ ID NO:1-79, and fragments thereof. The invention also provides an

isolated and purified polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-79, and fragments thereof. The invention also includes an isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-79, and fragments thereof.

Additionally, the invention provides an isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-79, and fragments thereof. The invention also provides an isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide encoding the polypeptide comprising the amino acid sequence selected from the group consisting of SEQ ID NO:1-79, and fragments thereof.

The invention also provides an isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:134, SEQ ID NO:135, SEQ ID NO:136, SEQ ID NO:137, SEQ ID NO:138, SEQ ID NO:139, SEQ ID NO:140, SEQ ID NO:141, SEQ ID NO:142, SEQ ID NO:143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:154, SEQ ID NO:155, SEQ ID NO:156, SEQ ID NO:157, and SEQ ID NO:158 (SEQ ID NO:80-158), and fragments thereof. The invention further provides an isolated and purified polynucleotide variant having at least

90% polynucleotide sequence identity to the polynucleotide sequence selected from the group consisting of SEQ ID NO:80-158, and fragments thereof. The invention also provides an isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:80-158, and fragments thereof.

The invention also provides a method for detecting a polynucleotide in a sample containing nucleic acids, the method comprising the steps of (a) hybridizing the complement of the polynucleotide sequence to at least one of the polynucleotides of the sample, thereby forming a hybridization complex; and (b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of a polynucleotide in the sample. In one aspect, the method further comprises amplifying the polynucleotide prior to hybridization.

The invention further provides an expression vector containing at least a fragment of the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-79, and fragments thereof. In another aspect, the expression vector is contained within a host cell.

The invention also provides a method for producing a polypeptide, the method comprising the steps of: (a) culturing the host cell containing an expression vector containing at least a fragment of a polynucleotide under conditions suitable for the expression of the polypeptide; and (b) recovering the polypeptide from the host cell culture.

The invention also provides a pharmaceutical composition comprising a substantially purified polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:1-79, and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention further includes a purified antibody which binds to a polypeptide selected from the group consisting of SEQ ID NO:1-79, and fragments thereof. The invention also provides a purified agonist and a purified antagonist to the polypeptide.

The invention also provides a method for treating or preventing a disorder associated with decreased expression or activity of HTMPN, the method comprising administering to a subject in need of such treatment an effective amount of a pharmaceutical composition comprising a substantially purified polypeptide having the

amino acid sequence selected from the group consisting of SEQ ID NO:1-79, and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention also provides a method for treating or preventing a disorder associated with increased expression or activity of HTMPN, the method comprising administering to a subject in need of such treatment an effective amount of an antagonist of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-79, and fragments thereof.

BRIEF DESCRIPTION OF THE TABLES

Table 1 shows nucleotide and polypeptide sequence identification numbers (SEQ ID NOs), clone identification numbers (clone ID), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding HTMPN.

Table 2 shows features of each polypeptide sequence including predicted transmembrane sequences, potential motifs, homologous sequences, and methods and algorithms used for identification of HTMPN.

Table 3 shows the tissue-specific expression patterns of each nucleic acid sequence as determined by northern analysis, diseases, disorders, or conditions associated with these tissues, and the vector into which each cDNA was cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which Incyte cDNA clones encoding HTMPN were isolated.

Table 5 shows the programs, their descriptions, references, and threshold parameters used to analyze HTMPN.

DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise.

Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

DEFINITIONS

"HTMPN" refers to the amino acid sequences of substantially purified HTMPN obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and preferably the human species, from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term "agonist" refers to a molecule which, when bound to HTMPN, increases or prolongs the duration of the effect of HTMPN. Agonists may include proteins, nucleic acids, carbohydrates, or any other molecules which bind to and modulate the effect of HTMPN.

An "allelic variant" is an alternative form of the gene encoding HTMPN. Allelic variants may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. Any given natural or recombinant gene may have none, one, or many allelic forms. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

"Altered" nucleic acid sequences encoding HTMPN include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polynucleotide the same as HTMPN or a polypeptide with at least one functional characteristic of

HTMPN. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding HTMPN, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding HTMPN. The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent HTMPN. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of HTMPN is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, positively charged amino acids may include lysine and arginine, and amino acids with uncharged polar head groups having similar hydrophilicity values may include leucine, isoleucine, and valine; glycine and alanine; asparagine and glutamine; serine and threonine; and phenylalanine and tyrosine.

The terms “amino acid” or “amino acid sequence” refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. In this context, “fragments,” “immunogenic fragments,” or “antigenic fragments” refer to fragments of HTMPN which are preferably at least 5 to about 15 amino acids in length, most preferably at least 14 amino acids, and which retain some biological activity or immunological activity of HTMPN. Where “amino acid sequence” is recited to refer to an amino acid sequence of a naturally occurring protein molecule, “amino acid sequence” and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

“Amplification” relates to the production of additional copies of a nucleic acid sequence. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

The term “antagonist” refers to a molecule which, when bound to HTMPN, decreases the amount or the duration of the effect of the biological or immunological activity of HTMPN. Antagonists may include proteins, nucleic acids, carbohydrates, antibodies, or any other molecules which decrease the effect of HTMPN.

The term “antibody” refers to intact molecules as well as to fragments thereof, such

as Fab, $F(ab')_2$, and Fv fragments, which are capable of binding the epitopic determinant. Antibodies that bind HTMPN polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

The term "antigenic determinant" refers to that fragment of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (given regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.

The term "antisense" refers to any composition containing a nucleic acid sequence which is complementary to the "sense" strand of a specific nucleic acid sequence. Antisense molecules may be produced by any method including synthesis or transcription. Once introduced into a cell, the complementary nucleotides combine with natural sequences produced by the cell to form duplexes and to block either transcription or translation. The designation "negative" can refer to the antisense strand, and the designation "positive" can refer to the sense strand.

The term "biologically active," refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" refers to the capability of the natural, recombinant, or synthetic HTMPN, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

The terms "complementary" or "complementarity" refer to the natural binding of polynucleotides by base pairing. For example, the sequence "5' A-G-T 3'" bonds to the complementary sequence "3' T-C-A 5'." Complementarity between two single-stranded molecules may be "partial," such that only some of the nucleic acids bind, or it may be "complete," such that total complementarity exists between the single stranded molecules.

The degree of complementarity between nucleic acid strands has significant effects on the efficiency and strength of the hybridization between the nucleic acid strands. This is of particular importance in amplification reactions, which depend upon binding between nucleic acids strands, and in the design and use of peptide nucleic acid (PNA) molecules.

A "composition comprising a given polynucleotide sequence" or a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding HTMPN or fragments of HTMPN may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence"refers to a nucleic acid sequence which has been resequenced to resolve uncalled bases, extended using XL-PCR kit (Perkin-Elmer, Norwalk CT) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from the overlapping sequences of more than one Incyte Clone using a computer program for fragment assembly, such as the GELVIEW Fragment Assembly system (GCG, Madison WI). Some sequences have been both extended and assembled to produce the consensus sequence.

The term "correlates with expression of a polynucleotide" indicates that the detection of the presence of nucleic acids, the same or related to a nucleic acid sequence encoding HTMPN, by northern analysis is indicative of the presence of nucleic acids encoding HTMPN in a sample, and thereby correlates with expression of the transcript from the polynucleotide encoding HTMPN.

A "deletion"refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to the chemical modification of a polypeptide sequence, or a polynucleotide sequence. Chemical modifications of a polynucleotide sequence can include, for example, replacement of hydrogen by an alkyl, acyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is

one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

The term "similarity" refers to a degree of complementarity. There may be partial similarity or complete similarity. The word "identity" may substitute for the word "similarity." A partially complementary sequence that at least partially inhibits an identical sequence from hybridizing to a target nucleic acid is referred to as "substantially similar." The inhibition of hybridization of the completely complementary sequence to the target sequence may be examined using a hybridization assay (Southern or northern blot, solution hybridization, and the like) under conditions of reduced stringency. A substantially similar sequence or hybridization probe will compete for and inhibit the binding of a completely similar (identical) sequence to the target sequence under conditions of reduced stringency. This is not to say that conditions of reduced stringency are such that non-specific binding is permitted, as reduced stringency conditions require that the binding of two sequences to one another be a specific (i.e., a selective) interaction. The absence of non-specific binding may be tested by the use of a second target sequence which lacks even a partial degree of complementarity (e.g., less than about 30% similarity or identity). In the absence of non-specific binding, the substantially similar sequence or probe will not hybridize to the second non-complementary target sequence.

The phrases "percent identity" or "% identity" refer to the percentage of sequence similarity found in a comparison of two or more amino acid or nucleic acid sequences. Percent identity can be determined electronically, e.g., by using the MEGALIGN program (DNASTAR, Madison WI) which creates alignments between two or more sequences according to methods selected by the user, e.g., the clustal method. (See, e.g., Higgins, D.G. and P.M. Sharp (1988) Gene 73:237-244.) The clustal algorithm groups sequences into clusters by examining the distances between all pairs. The clusters are aligned pairwise and then in groups. The percentage similarity between two amino acid sequences, e.g., sequence A and sequence B, is calculated by dividing the length of sequence A, minus the number of gap residues in sequence A, minus the number of gap residues in sequence B, into the sum of the residue matches between sequence A and sequence B, times one hundred. Gaps of low or of no similarity between the two amino acid sequences are not included in determining percentage similarity. Percent identity between nucleic acid sequences can also be counted or calculated by other methods known

in the art, e.g., the Jotun Hein method. (See, e.g., Hein, J. (1990) Methods Enzymol. 183:626-645.) Identity between sequences can also be determined by other methods known in the art, e.g., by varying hybridization conditions.

"Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for stable mitotic chromosome segregation and maintenance.

The term "humanized antibody" refers to antibody molecules in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

"Hybridization" refers to any process by which a strand of nucleic acid binds with a complementary strand through base pairing.

The term "hybridization complex" refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g., C_0t or R_0t analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

The words "insertion" or "addition" refer to changes in an amino acid or nucleotide sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively, to the sequence found in the naturally occurring molecule.

"Immune response" can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

The term "microarray" refers to an arrangement of distinct polynucleotides on a substrate.

The terms "element" or "array element" in a microarray context, refer to hybridizable polynucleotides arranged on the surface of a substrate.

The term "modulate" refers to a change in the activity of HTMPN. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of HTMPN.

The phrases "nucleic acid" or "nucleic acid sequence" refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material. In this context, "fragments" refers to those nucleic acid sequences which, when translated, would produce polypeptides retaining some functional characteristic, e.g., antigenicity, or structural domain characteristic, e.g., ATP-binding site, of the full-length polypeptide.

The terms "operably associated" or "operably linked" refer to functionally related nucleic acid sequences. A promoter is operably associated or operably linked with a coding sequence if the promoter controls the translation of the encoded polypeptide. While operably associated or operably linked nucleic acid sequences can be contiguous and in the same reading frame, certain genetic elements, e.g., repressor genes, are not contiguously linked to the sequence encoding the polypeptide but still bind to operator sequences that control expression of the polypeptide.

The term "oligonucleotide" refers to a nucleic acid sequence of at least about 6 nucleotides to 60 nucleotides, preferably about 15 to 30 nucleotides, and most preferably about 20 to 25 nucleotides, which can be used in PCR amplification or in a hybridization assay or microarray. "Oligonucleotide" is substantially equivalent to the terms "amplimer," "primer," "oligomer," and "probe," as these terms are commonly defined in the art.

"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

The term "sample" is used in its broadest sense. A sample suspected of containing nucleic acids encoding HTMPN, or fragments thereof, or HTMPN itself, may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms “specific binding” or “specifically binding” refer to that interaction between a protein or peptide and an agonist, an antibody, or an antagonist. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope “A,” the presence of a polypeptide containing the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

The term “stringent conditions” refers to conditions which permit hybridization between polynucleotides and the claimed polynucleotides. Stringent conditions can be defined by salt concentration, the concentration of organic solvent, e.g., formamide, temperature, and other conditions well known in the art. In particular, stringency can be increased by reducing the concentration of salt, increasing the concentration of formamide, or raising the hybridization temperature.

The term “substantially purified” refers to nucleic acid or amino acid sequences that are removed from their natural environment and are isolated or separated, and are at least about 60% free, preferably about 75% free, and most preferably about 90% free from other components with which they are naturally associated.

A “substitution” refers to the replacement of one or more amino acids or nucleotides by different amino acids or nucleotides, respectively.

“Substrate” refers to any suitable rigid or semi-rigid support including membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

“Transformation” describes a process by which exogenous DNA enters and changes a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, viral infection, electroporation, heat shock, lipofection, and particle bombardment. The term "transformed" cells includes stably transformed cells in which the inserted DNA is capable of replication either as an

autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

A "variant" of HTMPN polypeptides refers to an amino acid sequence that is altered by one or more amino acid residues. The variant may have "conservative" changes, wherein a substituted amino acid has similar structural or chemical properties (e.g., replacement of leucine with isoleucine). More rarely, a variant may have "nonconservative" changes (e.g., replacement of glycine with tryptophan). Analogous minor variations may also include amino acid deletions or insertions, or both. Guidance in determining which amino acid residues may be substituted, inserted, or deleted without abolishing biological or immunological activity may be found using computer programs well known in the art, for example, LASERGENE software (DNASTAR).

The term "variant," when used in the context of a polynucleotide sequence, may encompass a polynucleotide sequence related to HTMPN. This definition may also include, for example, "allelic" (as defined above), "splice," "species," or "polymorphic" variants. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternate splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or an absence of domains. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

THE INVENTION

The invention is based on the discovery of new human transmembrane proteins (HTMPN), the polynucleotides encoding HTMPN, and the use of these compositions for the diagnosis, treatment, or prevention of immune, reproductive, smooth muscle, neurological, gastrointestinal, developmental, and cell proliferative disorders.

Table 1 lists the Incyte Clones used to derive full length nucleotide sequences encoding HTMPN. Columns 1 and 2 show the sequence identification numbers (SEQ ID

NOs) of the amino acid and nucleic acid sequences, respectively. Column 3 shows the Clone ID of the Incyte Clone in which nucleic acids encoding each HTMPN were identified, and column 4, the cDNA libraries from which these clones were isolated. Column 5 shows Incyte clones, their corresponding cDNA libraries, and shotgun sequences. The clones and shotgun sequences are part of the consensus nucleotide sequence of each HTMPN and are useful as fragments in hybridization technologies.

The columns of Table 2 show various properties of the polypeptides of the invention: column 1 references the SEQ ID NO; column 2 shows the number of amino acid residues in each polypeptide; column 3, potential phosphorylation sites; column 4, potential glycosylation sites; column 5, the amino acid residues comprising signature sequences and motifs; column 6, the identity of each protein; and column 7, analytical methods used to identify each protein through sequence homology and protein motifs. Hidden Markov Model analysis indicates the presence of one or more potential transmembrane motifs in each of SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO: 66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO: 75, SEQ ID NO:76, SEQ ID NO:77, and SEQ ID NO: 79; as well as the presence of one or more potential signal peptide motifs in each of SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:75, SEQ ID NO:77, and SEQ ID NO:79.

Motifs analysis indicates the presence of a potential ATP/GTP binding site in SEQ ID NO:68, a potential calcium-binding site also in SEQ ID NO:68, a potential leucine zipper gene regulatory motif in each of SEQ ID NO:68 and SEQ ID NO:73; and a potential microbody (single-membraned organelle) targeting signal site in SEQ ID NO:78. BLOCKS analysis indicates the presence of two potential PMP-22 integral membrane glycoprotein motifs and a trehalase motif, all in SEQ ID NO:77, as well as a potential protein-splicing motif in SEQ ID NO:66. PRINTS analysis indicates the presence of a potential G-protein coupled receptor motif in SEQ ID NO:79.

The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions associated with nucleotide sequences encoding HTMPN. The first column of Table 3 lists the nucleotide sequence identifiers. The second column lists tissue categories which express HTMPN as a fraction of total tissue categories expressing HTMPN. The

third column lists the diseases, disorders, or conditions associated with those tissues expressing HTMPN. The fourth column lists the vectors used to subclone the cDNA library. Of particular note is the expression of HTMPN in tissue involved in inflammation and the immune response and with cell proliferative conditions including cancer, and in reproductive, gastrointestinal, fetal, smooth muscle, cardiovascular, urologic, endocrine, developmental, and nervous tissue.

The following fragments of the nucleotide sequences encoding HTMPN are useful in hybridization or amplification technologies to identify SEQ ID NO:121-158 and to distinguish between SEQ ID NO:121-158 and related polynucleotide sequences. The useful fragments are the fragment of SEQ ID NO:121 from about nucleotide 151 to about nucleotide 189; the fragment of SEQ ID NO:122 from about nucleotide 280 to about nucleotide 318; the fragment of SEQ ID NO:123 from about nucleotide 505 to about nucleotide 558; the fragments of SEQ ID NO:124 from about nucleotide 1 to about nucleotide 21 and from about nucleotide 694 to about nucleotide 720; the fragment of SEQ ID NO:125 from about nucleotide 331 to about nucleotide 378; the fragment of SEQ ID NO:126 from about nucleotide 1012 to about nucleotide 1047; the fragment of SEQ ID NO:127 from about nucleotide 1070 to about nucleotide 1106; the fragment of SEQ ID NO:128 from about nucleotide 133 to about nucleotide 186; the fragment of SEQ ID NO:129 from about nucleotide 432 to about nucleotide 482; the fragments of SEQ ID NO:130 from about nucleotide 1745 to about nucleotide 1795 and from about nucleotide 1910 to about nucleotide 1979; the fragment of SEQ ID NO:131 from about nucleotide 322 to about nucleotide 375; the fragment of SEQ ID NO:132 from about nucleotide 147 to about nucleotide 203; the fragment of SEQ ID NO:133 from about nucleotide 557 to about nucleotide 613; the fragment of SEQ ID NO:134 from about nucleotide 509 to about nucleotide 595; the fragment of SEQ ID NO:135 from about nucleotide 808 to about nucleotide 848; the fragment of SEQ ID NO:136 from about nucleotide 216 to about nucleotide 260; the fragment of SEQ ID NO:137 from about nucleotide 132 to about nucleotide 188; the fragment of SEQ ID NO:138 from about nucleotide 231 to about nucleotide 278; the fragment of SEQ ID NO:139 from about nucleotide 303 to about nucleotide 350; the fragment of SEQ ID NO:140 from about nucleotide 507 to about nucleotide 550; the fragment of SEQ ID NO:141 from about nucleotide 433 to about nucleotide 477; the fragment of SEQ ID NO:142 from about nucleotide 266 to about

nucleotide 314; the fragment of SEQ ID:143 from about nucleotide 3 to about nucleotide 48; the fragment of SEQ ID NO:144 from about nucleotide 76 to about nucleotide 122; the fragment of SEQ ID NO:145 from about nucleotide 93 to about nucleotide 139; the fragment of SEQ ID NO:146 from about nucleotide 241 to about nucleotide 286; the fragment of SEQ ID NO:147 from about nucleotide 43 to about nucleotide 89; the fragment of SEQ ID NO:148 from about nucleotide 219 to about nucleotide 265; the fragment of SEQ ID NO:149 from about nucleotide 619 to about nucleotide 663; the fragment of SEQ ID NO:150 from about nucleotide 25 to about nucleotide 69; the fragment of SEQ ID NO:151 from about nucleotide 175 to about nucleotide 221; the fragment of SEQ ID NO:152 from about nucleotide 94 to about nucleotide 138; the fragment of SEQ ID NO:153 from about nucleotide 46 to about nucleotide 90; the fragment of SEQ ID NO:154 from about nucleotide 1081 to about nucleotide 1127; the fragment of SEQ ID NO:155 from about nucleotide 31 to about nucleotide 77; the fragment of SEQ ID NO:156 from about nucleotide 157 to about nucleotide 201; the fragment of SEQ ID NO:157 from about nucleotide 216 to about nucleotide 259; and the fragment of SEQ ID NO:158 from about nucleotide 517 to about nucleotide 561. The polypeptides encoded by these fragments may be useful, for example, as antigenic polypeptides.

The invention also encompasses HTMPN variants. A preferred HTMPN variant is one which has at least about 80%, more preferably at least about 90%, and most preferably at least about 95% amino acid sequence identity to the HTMPN amino acid sequence, and which contains at least one functional or structural characteristic of HTMPN.

The invention also encompasses polynucleotides which encode HTMPN. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:80-158, which encodes HTMPN.

The invention also encompasses a variant of a polynucleotide sequence encoding HTMPN. In particular, such a variant polynucleotide sequence will have at least about 80%, more preferably at least about 90%, and most preferably at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding HTMPN. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:80-158 which

has at least about 80%, more preferably at least about 90%, and most preferably at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:80-158. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of HTMPN.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding HTMPN, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring HTMPN, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode HTMPN and its variants are preferably capable of hybridizing to the nucleotide sequence of the naturally occurring HTMPN under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding HTMPN or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding HTMPN and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode HTMPN and HTMPN derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding HTMPN or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:80-158 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) Methods Enzymol. 152:399-407; Kimmel, A.R. (1987) Methods Enzymol. 152:507-511.) For example, stringent salt concentration will ordinarily be less than about 750 mM NaCl and 75 mM trisodium citrate, preferably less than about 500 mM NaCl and 50 mM trisodium citrate, and most preferably less than about 250 mM NaCl and 25 mM trisodium citrate. Low stringency hybridization can be obtained in the absence of organic solvent, e.g., formamide, while high stringency hybridization can be obtained in the presence of at least about 35% formamide, and most preferably at least about 50% formamide. Stringent temperature conditions will ordinarily include temperatures of at least about 30°C, more preferably of at least about 37°C, and most preferably of at least about 42°C. Varying additional parameters, such as hybridization time, the concentration of detergent, e.g., sodium dodecyl sulfate (SDS), and the inclusion or exclusion of carrier DNA, are well known to those skilled in the art.. Various levels of stringency are accomplished by combining these various conditions as needed. In a preferred embodiment, hybridization will occur at 30°C in 750 mM NaCl, 75 mM trisodium citrate, and 1% SDS. In a more preferred embodiment, hybridization will occur at 37°C in 500 mM NaCl, 50 mM trisodium citrate, 1% SDS, 35% formamide, and 100 μg/ml denatured salmon sperm DNA (ssDNA). In a most preferred embodiment, hybridization will occur at 42°C in 250 mM NaCl, 25 mM trisodium citrate, 1% SDS, 50 % formamide, and 200 μg/ml ssDNA. Useful variations on these conditions will be readily apparent to those skilled in the art.

The washing steps which follow hybridization can also vary in stringency. Wash stringency conditions can be defined by salt concentration and by temperature. As above, wash stringency can be increased by decreasing salt concentration or by increasing temperature. For example, stringent salt concentration for the wash steps will preferably be less than about 30 mM NaCl and 3 mM trisodium citrate, and most preferably less than about 15 mM NaCl and 1.5 mM trisodium citrate. Stringent temperature conditions for the wash steps will ordinarily include temperature of at least about 25°C, more preferably of at least about 42°C, and most preferably of at least about 68°C. In a preferred embodiment, wash steps will occur at 25°C in 30 mM NaCl, 3 mM trisodium citrate, and 0.1% SDS. In

a more preferred embodiment, wash steps will occur at 42°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. In a most preferred embodiment, wash steps will occur at 68°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. Additional variations on these conditions will be readily apparent to those skilled in the art.

Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (Perkin-Elmer), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the Hamilton MICROLAB 2200 (Hamilton, Reno NV), Peltier Thermal Cycler 200 (PTC200; MJ Research, Watertown MA) and the ABI CATALYST 800 (Perkin-Elmer). Sequencing is then carried out using either ABI 373 or 377 DNA sequencing systems (Perkin-Elmer) or the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA). The resulting sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

The nucleic acid sequences encoding HTMPN may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) PCR Methods Applic. 2:318-322.) Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) Nucleic Acids Res. 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom, M. et al. (1991) PCR Methods Applic. 1:111-119.) In this

method, multiple restriction enzyme digestions and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) Nucleic Acids Res. 19:3055-306). Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 Primer Analysis software (National Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

When screening for full-length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, Perkin-Elmer), and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode HTMPN may be cloned in recombinant DNA molecules that direct expression of HTMPN, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express HTMPN.

The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter HTMPN-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

In another embodiment, sequences encoding HTMPN may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucl. Acids Res. Symp. Ser. 215-223, and Horn, T. et al. (1980) Nucl. Acids Res. Symp. Ser. 225-232.) Alternatively, HTMPN itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solid-phase techniques. (See, e.g., Roberge, J.Y. et al. (1995) Science 269:202-204.) Automated synthesis may be achieved using the ABI 431A Peptide Synthesizer (Perkin-Elmer). Additionally, the amino acid sequence of HTMPN, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g, Chiez, R.M. and F.Z. Regnier (1990) Methods Enzymol. 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH Freeman, New York NY.)

In order to express a biologically active HTMPN, the nucleotide sequences encoding HTMPN or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding HTMPN. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding HTMPN. Such signals include the ATG initiation codon and adjacent sequences, e.g. the

Kozak sequence. In cases where sequences encoding HTMPN and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) Results Probl. Cell Differ. 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding HTMPN and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding HTMPN. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus,TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding HTMPN. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding HTMPN can be achieved using a multifunctional E. coli vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or pSPORT1 plasmid (Life Technologies). Ligation of sequences encoding HTMPN into the vector's multiple cloning site disrupts the *lac*Z gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be

useful for in vitro transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509.) When large quantities of HTMPN are needed, e.g. for the production of antibodies, vectors which direct high level expression of HTMPN may be used. For example, vectors containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of HTMPN. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH, may be used in the yeast Saccharomyces cerevisiae or Pichia pastoris. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, supra; Grant et al. (1987) Methods Enzymol. 153:516-54; and Scorer, C. A. et al. (1994) Bio/Technology 12:181-184.)

Plant systems may also be used for expression of HTMPN. Transcription of sequences encoding HTMPN may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al. (1984) Science 224:838-843; and Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105.) These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, sequences encoding HTMPN may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses HTMPN in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of HTMPN in cell lines is preferred. For example, sequences encoding HTMPN can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk*⁻ or *apr*⁻ cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides, neomycin and G-418; and *als* or *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech), ß glucuronidase and its substrate ß-glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding HTMPN is inserted within a marker gene sequence, transformed cells containing sequences encoding HTMPN can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding HTMPN under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

In general, host cells that contain the nucleic acid sequence encoding HTMPN and that express HTMPN may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

Immunological methods for detecting and measuring the expression of HTMPN using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on HTMPN is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St Paul MN, Sect. IV; Coligan, J. E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ).

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding HTMPN include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding HTMPN, or any fragments thereof, may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be

used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding HTMPN may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode HTMPN may be designed to contain signal sequences which direct secretion of HTMPN through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38), are available from the American Type Culture Collection (ATCC, Bethesda MD) and may be chosen to ensure the correct modification and processing of the foreign protein.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding HTMPN may be ligated to a heterologous sequence resulting in translation of a fusion protein in any of the aforementioned host systems. For example, a chimeric HTMPN protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of HTMPN activity. Heterologous protein and peptide moieties may also facilitate purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose

binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the HTMPN encoding sequence and the heterologous protein sequence, so that HTMPN may be cleaved away from the heterologous moiety following purification. Methods for fusion protein expression and purification are discussed in Ausubel (1995, supra, ch 10). A variety of commercially available kits may also be used to facilitate expression and purification of fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled HTMPN may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract systems (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, preferably ^{35}S-methionine.

Fragments of HTMPN may be produced not only by recombinant production, but also by direct peptide synthesis using solid-phase techniques. (See, e.g., Creighton, supra, pp. 55-60.) Protein synthesis may be performed by manual techniques or by automation. Automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin-Elmer). Various fragments of HTMPN may be synthesized separately and then combined to produce the full length molecule.

THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of HTMPN and human transmembrane proteins. In addition, the expression of HTMPN is closely associated with tissue involved in inflammation and the immune response and with cell proliferative conditions including cancer, and in reproductive, gastrointestinal, fetal, smooth muscle, cardiovascular, developmental, and nervous tissue. Therefore, HTMPN appears to play a role in immune, reproductive, smooth muscle, neurological, gastrointestinal, developmental, and cell proliferative disorders. In the treatment of immune, reproductive, smooth muscle, neurological,

gastrointestinal, developmental, and cell proliferative disorders associated with increased HTMPN expression or activity, it is desirable to decrease the expression or activity of HTMPN. In the treatment of the above conditions associated with decreased HTMPN expression or activity, it is desirable to increase the expression or activity of HTMPN.

Therefore, in one embodiment, HTMPN or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of HTMPN. Examples of such disorders include, but are not limited to, an immune disorder such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyenodocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; a reproductive disorder such as a a disorder of prolactin production; infertility, including tubal disease, ovulatory defects, and endometriosis; a disruption of the estrous cycle, a disruption of the menstrual cycle, polycystic ovary syndrome, ovarian hyperstimulation syndrome, endometrial and ovarian tumors, uterine fibroids, autoimmune disorders, ectopic pregnancies, and teratogenesis; cancer of the breast, fibrocystic breast disease, and galactorrhea; disruptions of spermatogenesis, abnormal sperm physiology, cancer of the testis, cancer of the prostate, benign prostatic hyperplasia, prostatitis, Peyronie's disease, impotence, carcinoma of the male breast, and gynecomastia; a smooth muscle disorder such as angina, anaphylactic shock, arrhythmias, asthma, cardiovascular shock, Cushing's syndrome, hypertension, hypoglycemia, myocardial infarction, migraine, and pheochromocytoma, and myopathies

including cardiomyopathy, encephalopathy, epilepsy, Kearns-Sayre syndrome, lactic acidosis, myoclonic disorder, and ophthalmoplegia; a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease; prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome; fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system disorders, dermatomyositis and polymyositis; inherited, metabolic, endocrine, and toxic myopathies; myasthenia gravis, periodic paralysis; mental disorders including mood, anxiety, and schizophrenic disorders; akathesia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, and Tourette's disorder; a gastrointestinal disorder such as dysphagia, peptic esophagitis, esophageal spasm, esophageal stricture, esophageal carcinoma, dyspepsia, indigestion, gastritis, gastric carcinoma, anorexia, nausea, emesis, gastroparesis, antral or pyloric edema, abdominal angina, pyrosis, gastroenteritis, intestinal obstruction, infections of the intestinal tract, peptic ulcer, cholelithiasis, cholecystitis, cholestasis, pancreatitis, pancreatic carcinoma, biliary tract disease, hepatoma, infectious colitis, ulcerative colitis, ulcerative proctitis, Crohn's disease, Whipple's disease, Mallory-Weiss syndrome, colonic carcinoma, colonic obstruction, irritable bowel syndrome, short bowel syndrome, diarrhea, constipation, gastrointestinal hemorrhage, and acquired immunodeficiency syndrome (AIDS) enteropathy, cirrhosis, jaundice, cholestasis, hereditary hyperbilirubinemia, hepatic encephalopathy, hepatorenal syndrome, hepatitis, hepatic steatosis, hemochromatosis, Wilson's disease, α_1-antitrypsin deficiency, Reye's syndrome, primary sclerosing cholangitis, liver infarction, portal vein obstruction and

thrombosis, passive congestion, centrilobular necrosis, peliosis hepatis, hepatic vein thrombosis, veno-occlusive disease, preeclampsia, eclampsia, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, and hepatic tumors including nodular hyperplasias, adenomas, and carcinomas; a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; and a developmental disorder including, but not limited to, those listed above.

In another embodiment, a vector capable of expressing HTMPN or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of HTMPN including, but not limited to, those described above.

In a further embodiment, a pharmaceutical composition comprising a substantially purified HTMPN in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of HTMPN including, but not limited to, those provided above.

In still another embodiment, an agonist which modulates the activity of HTMPN may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of HTMPN including, but not limited to, those listed above.

In a further embodiment, an antagonist of HTMPN may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of HTMPN. Examples of such disorders include, but are not limited to, those described above. In one aspect, an antibody which specifically binds HTMPN may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissue which express HTMPN.

In an additional embodiment, a vector expressing the complement of the polynucleotide encoding HTMPN may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of HTMPN including, but not

limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of HTMPN may be produced using methods which are generally known in the art. In particular, purified HTMPN may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind HTMPN. Antibodies to HTMPN may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are especially preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with HTMPN or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to HTMPN have an amino acid sequence consisting of at least about 5 amino acids, and, more preferably, of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein and contain the entire amino acid sequence of a small, naturally occurring molecule. Short stretches of HTMPN amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be

produced.

Monoclonal antibodies to HTMPN may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. 80:2026-2030; and Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda, S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce HTMPN-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton D.R. (1991) Proc. Natl. Acad. Sci. 88:10134-10137.)

Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. 86: 3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for HTMPN may also be generated. For example, such fragments include, but are not limited to, F(ab')2 fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the F(ab')2 fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D. et al. (1989) Science 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are

well known in the art. Such immunoassays typically involve the measurement of complex formation between HTMPN and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering HTMPN epitopes is preferred, but a competitive binding assay may also be employed (Pound, supra).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for HTMPN. Affinity is expressed as an association constant, K_a, which is defined as the molar concentration of HTMPN-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The K_a determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple HTMPN epitopes, represents the average affinity, or avidity, of the antibodies for HTMPN. The K_a determined for a preparation of monoclonal antibodies, which are monospecific for a particular HTMPN epitope, represents a true measure of affinity. High-affinity antibody preparations with K_a ranging from about 10^9 to 10^{12} L/mole are preferred for use in immunoassays in which the HTMPN-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with K_a ranging from about 10^6 to 10^7 L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of HTMPN, preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington, DC; Liddell. J. E. and Cryer, A. (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg specific antibody/ml, is preferred for use in procedures requiring precipitation of HTMPN-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al. supra.)

In another embodiment of the invention, the polynucleotides encoding HTMPN, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect,

the complement of the polynucleotide encoding HTMPN may be used in situations in which it would be desirable to block the transcription of the mRNA. In particular, cells may be transformed with sequences complementary to polynucleotides encoding HTMPN. Thus, complementary molecules or fragments may be used to modulate HTMPN activity, or to achieve regulation of gene function. Such technology is now well known in the art, and sense or antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding HTMPN.

Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. Methods which are well known to those skilled in the art can be used to construct vectors to express nucleic acid sequences complementary to the polynucleotides encoding HTMPN. (See, e.g., Sambrook, supra; Ausubel, 1995, supra.)

Genes encoding HTMPN can be turned off by transforming a cell or tissue with expression vectors which express high levels of a polynucleotide, or fragment thereof, encoding HTMPN. Such constructs may be used to introduce untranslatable sense or antisense sequences into a cell. Even in the absence of integration into the DNA, such vectors may continue to transcribe RNA molecules until they are disabled by endogenous nucleases. Transient expression may last for a month or more with a non-replicating vector, and may last even longer if appropriate replication elements are part of the vector system.

As mentioned above, modifications of gene expression can be obtained by designing complementary sequences or antisense molecules (DNA, RNA, or PNA) to the control, 5', or regulatory regions of the gene encoding HTMPN. Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, are preferred. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block

translation of mRNA by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding HTMPN.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding HTMPN. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nature Biotechnology 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as dogs, cats, cows, horses, rabbits, monkeys, and most preferably, humans.

An additional embodiment of the invention relates to the administration of a pharmaceutical or sterile composition, in conjunction with a pharmaceutically acceptable carrier, for any of the therapeutic effects discussed above. Such pharmaceutical compositions may consist of HTMPN, antibodies to HTMPN, and mimetics, agonists, antagonists, or inhibitors of HTMPN. The compositions may be administered alone or in combination with at least one other agent, such as a stabilizing compound, which may be administered in any sterile, biocompatible pharmaceutical carrier including, but not limited to, saline, buffered saline, dextrose, and water. The compositions may be administered to a patient alone, or in combination with other agents, drugs, or hormones.

The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA).

Pharmaceutical compositions for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for

ingestion by the patient.

Pharmaceutical preparations for oral use can be obtained through combining active compounds with solid excipient and processing the resultant mixture of granules (optionally, after grinding) to obtain tablets or dragee cores. Suitable auxiliaries can be added, if desired. Suitable excipients include carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, and sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; gums, including arabic and tragacanth; and proteins, such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, and alginic acid or a salt thereof, such as sodium alginate.

Dragee cores may be used in conjunction with suitable coatings, such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, i.e., dosage.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with fillers or binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with or without stabilizers.

Pharmaceutical formulations suitable for parenteral administration may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiologically buffered saline. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils, such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate, triglycerides, or liposomes. Non-lipid polycationic amino

polymers may also be used for delivery. Optionally, the suspension may also contain suitable stabilizers or agents to increase the solubility of the compounds and allow for the preparation of highly concentrated solutions.

For topical or nasal administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes.

The pharmaceutical composition may be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, and succinic acid. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. In other cases, the preferred preparation may be a lyophilized powder which may contain any or all of the following: 1 mM to 50 mM histidine, 0.1% to 2% sucrose, and 2% to 7% mannitol, at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

After pharmaceutical compositions have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. For administration of HTMPN, such labeling would include amount, frequency, and method of administration.

Pharmaceutical compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells or in animal models such as mice, rats, rabbits, dogs, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example HTMPN or fragments thereof, antibodies of HTMPN, and agonists, antagonists

or inhibitors of HTMPN, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating the ED_{50} (the dose therapeutically effective in 50% of the population) or LD_{50} (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, and it can be expressed as the LD_{50}/ED_{50} ratio. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that includes the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from about 0.1 μg to 100,000 μg, up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

DIAGNOSTICS

In another embodiment, antibodies which specifically bind HTMPN may be used for the diagnosis of disorders characterized by expression of HTMPN, or in assays to monitor patients being treated with HTMPN or agonists, antagonists, or inhibitors of HTMPN. Antibodies useful for diagnostic purposes may be prepared in the same manner

as described above for therapeutics. Diagnostic assays for HTMPN include methods which utilize the antibody and a label to detect HTMPN in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

A variety of protocols for measuring HTMPN, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of HTMPN expression. Normal or standard values for HTMPN expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to HTMPN under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, preferably by photometric means. Quantities of HTMPN expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

In another embodiment of the invention, the polynucleotides encoding HTMPN may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantitate gene expression in biopsied tissues in which expression of HTMPN may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess expression of HTMPN, and to monitor regulation of HTMPN levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding HTMPN or closely related molecules may be used to identify nucleic acid sequences which encode HTMPN. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification (maximal, high, intermediate, or low), will determine whether the probe identifies only naturally occurring sequences encoding HTMPN, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and should

preferably have at least 50% sequence identity to any of the HTMPN encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:80-158 or from genomic sequences including promoters, enhancers, and introns of the HTMPN gene.

Means for producing specific hybridization probes for DNAs encoding HTMPN include the cloning of polynucleotide sequences encoding HTMPN or HTMPN derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety of reporter groups, for example, by radionuclides such as ^{32}P or ^{35}S, or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

Polynucleotide sequences encoding HTMPN may be used for the diagnosis of disorders associated with expression of HTMPN. Examples of such disorders include, but are not limited to, an immune disorder such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyenodocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; a reproductive disorder such as a a disorder of prolactin production; infertility, including tubal disease, ovulatory defects, and endometriosis; a disruption of the estrous cycle, a disruption of the menstrual cycle, polycystic ovary syndrome, ovarian hyperstimulation syndrome, endometrial and ovarian

tumors, uterine fibroids, autoimmune disorders, ectopic pregnancies, and teratogenesis; cancer of the breast, fibrocystic breast disease, and galactorrhea; disruptions of spermatogenesis, abnormal sperm physiology, cancer of the testis, cancer of the prostate, benign prostatic hyperplasia, prostatitis, Peyronie's disease, impotence, carcinoma of the male breast, and gynecomastia; a smooth muscle disorder such as angina, anaphylactic shock, arrhythmias, asthma, cardiovascular shock, Cushing's syndrome, hypertension, hypoglycemia, myocardial infarction, migraine, and pheochromocytoma, and myopathies including cardiomyopathy, encephalopathy, epilepsy, Kearns-Sayre syndrome, lactic acidosis, myoclonic disorder, and ophthalmoplegia; a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease; prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome; fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system disorders, dermatomyositis and polymyositis; inherited, metabolic, endocrine, and toxic myopathies; myasthenia gravis, periodic paralysis; mental disorders including mood, anxiety, and schizophrenic disorders; akathesia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, and Tourette's disorder; a gastrointestinal disorder such as dysphagia, peptic esophagitis, esophageal spasm, esophageal stricture, esophageal carcinoma, dyspepsia, indigestion, gastritis, gastric carcinoma, anorexia, nausea, emesis, gastroparesis, antral or pyloric edema, abdominal angina, pyrosis, gastroenteritis, intestinal obstruction, infections of the intestinal tract, peptic ulcer, cholelithiasis, cholecystitis, cholestasis, pancreatitis, pancreatic carcinoma, biliary tract disease, hepatoma, infectious

colitis, ulcerative colitis, ulcerative proctitis, Crohn's disease, Whipple's disease, Mallory-Weiss syndrome, colonic carcinoma, colonic obstruction, irritable bowel syndrome, short bowel syndrome, diarrhea, constipation, gastrointestinal hemorrhage, and acquired immunodeficiency syndrome (AIDS) enteropathy, cirrhosis, jaundice, cholestasis, hereditary hyperbilirubinemia, hepatic encephalopathy, hepatorenal syndrome, hepatitis, hepatic steatosis, hemochromatosis, Wilson's disease, α_1-antitrypsin deficiency, Rèye's syndrome, primary sclerosing cholangitis, liver infarction, portal vein obstruction and thrombosis, passive congestion, centrilobular necrosis, peliosis hepatis, hepatic vein thrombosis, veno-occlusive disease, preeclampsia, eclampsia, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, and hepatic tumors including nodular hyperplasias, adenomas, and carcinomas; a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; and a developmental disorder including, but not limited to, those listed above. The polynucleotide sequences encoding HTMPN may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered HTMPN expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding HTMPN may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide sequences encoding HTMPN may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantitated and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding HTMPN in the sample indicates the

presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with expression of HTMPN, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding HTMPN, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding HTMPN may involve the use of PCR. These oligomers may be chemically synthesized, generated enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding HTMPN, or a fragment of a polynucleotide complementary to the polynucleotide encoding HTMPN, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or

quantitation of closely related DNA or RNA sequences.

Methods which may also be used to quantitate the expression of HTMPN include radiolabeling or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C. et al. (1993) Anal. Biochem. 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in an ELISA format where the oligomer of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantitation.

In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as targets in a microarray. The microarray can be used to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, and to develop and monitor the activities of therapeutic agents.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.)

In another embodiment of the invention, nucleic acid sequences encoding HTMPN may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical chromosome mapping techniques and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, supra, pp. 965-968.) Examples of genetic map data can be found in

various scientific journals or at the Online Mendelian Inheritance in Man (OMIM) site. Correlation between the location of the gene encoding HTMPN on a physical chromosomal map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder. The nucleotide sequences of the invention may be used to detect differences in gene sequences among normal, carrier, and affected individuals.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the number or arm of a particular human chromosome is not known. New sequences can be assigned to chromosomal arms by physical mapping. This provides valuable information to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the disease or syndrome has been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the subject invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

In another embodiment of the invention, HTMPN, its catalytic or immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between HTMPN and the agent being tested may be measured.

Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with HTMPN, or fragments thereof, and washed. Bound HTMPN is then detected by methods well known in the art. Purified HTMPN can also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing

antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding HTMPN specifically compete with a test compound for binding HTMPN. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with HTMPN.

In additional embodiments, the nucleotide sequences which encode HTMPN may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The entire disclosure of all applications, patents, and publications, cited above and below, and of US provisional applications 60/087,260 (filed May 29, 1998), 60/091,674 (filed July 2, 1998), 60/102.954 (filed October 2, 1998), and 60/109,869 (filed November 24, 1998) is hereby incorporated by reference.

EXAMPLES

I. Construction of cDNA Libraries

RNA was purchased from Clontech or isolated from tissues described in Table 4. Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA purity. In some cases, RNA was treated with DNase. For most libraries, poly(A+) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Valencia CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates

using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERSCRIPT plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, supra, units 5.1-6.6). Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUESCRIPT plasmid (Stratagene), pSPORT1 plasmid (Life Technologies), or pINCY (Incyte Pharmaceuticals, Palo Alto CA). Recombinant plasmids were transformed into competent E. coli cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5α, DH10B, or ElectroMAX DH10B from Life Technologies.

II. Isolation of cDNA Clones

Plasmids were recovered from host cells by in vivo excision, using the UNIZAP vector system (Stratagene) or cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the REAL Prep 96 plasmid kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using PICOGREEN dye (Molecular Probes, Eugene OR) and a Fluoroskan II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

III. Sequencing and Analysis

The cDNAs were prepared for sequencing using the ABI CATALYST 800 (Perkin-Elmer) or the HYDRA microdispenser (Robbins Scientific) or MICROLAB 2200 (Hamilton) systems in combination with the PTC-200 thermal cyclers (MJ Research). The cDNAs were sequenced using the ABI PRISM 373 or 377 sequencing systems (Perkin-Elmer) and standard ABI protocols, base calling software, and kits. In one alternative, cDNAs were sequenced using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics). In another alternative, the cDNAs were amplified and sequenced using the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer). In yet another alternative, cDNAs were sequenced using solutions and dyes from Amersham Pharmacia Biotech. Reading frames for the ESTs were determined using standard methods (reviewed in Ausubel, 1997, supra, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example V.

The polynucleotide sequences derived from cDNA, extension, and shotgun sequencing were assembled and analyzed using a combination of software programs which utilize algorithms well known to those skilled in the art. Table 5 summarizes the software programs, descriptions, references, and threshold parameters used. The first column of Table 5 shows the tools, programs, and algorithms used, the second column provides a brief description thereof, the third column presents the references which are incorporated by reference herein, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the probability the greater the homology). Sequences were analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR).

The polynucleotide sequences were validated by removing vector, linker, and polyA sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programing, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases such as GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS to acquire annotation, using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled into full length polynucleotide sequences using programs based on Phred, Phrap, and Consed, and were screened for open reading frames using programs based on

GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying against databases such as the GenBank databases (described above), SwissProt, BLOCKS, PRINTS, Prosite, and Hidden Markov Model (HMM)-based protein family databases such as PFAM. HMM is a probalistic approach which analyzes consensus primary structures of gene families. (See, e.g., Eddy, S.R. (1996) Cur. Opin. Str. Biol. 6:361-365.)

The programs described above for the assembly and analysis of full length polynucleotide and amino acid sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:80-158. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies were described in The Invention section above.

IV. Northern Analysis

Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7; Ausubel, 1995, supra, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in nucleotide databases such as GenBank or LIFESEQ database (Incyte Pharmaceuticals). This analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

$$\frac{\%\ \text{sequence identity} \times \%\ \text{maximum BLAST score}}{100}$$

The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. For example, with a product score of 40, the match will be exact within a 1% to 2% error, and, with a product score of 70, the match will be exact. Similar molecules are usually identified by selecting those which show product scores between 15 and 40, although lower scores may identify related molecules.

The results of northern analyses are reported as a percentage distribution of libraries in which the transcript encoding HTMPN occurred. Analysis involved the

categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic, developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease/condition categories included cancer, inflammation/trauma, cell proliferation, neurological, and pooled. For each category, the number of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories. Percentage values of tissue-specific and disease- or condition-specific expression are reported in Table 3.

V. Extension of HTMPN Encoding Polynucleotides

Full length nucleic acid sequences of SEQ ID NOs:80-120 were produced by extension of the component fragments described in Table 1, column 5, using oligonucleotide primers based on these fragments. For each nucleic acid sequence, one primer was synthesized to initiate extension of an antisense polynucleotide, and the other was synthesized to initiate extension of a sense polynucleotide. Primers were used to facilitate the extension of the known sequence "outward" generating amplicons containing new unknown nucleotide sequence for the region of interest. The initial primers were designed from the cDNA using OLIGO™ 4.06 (National Biosciences, Plymouth, MN), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries (GIBCO BRL) were used to extend the sequence. If more than one extension is necessary or desired, additional sets of primers are designed to further extend the known region.

High fidelity amplification was obtained by following the instructions for the XL-PCR™ kit (The Perkin-Elmer Corp., Norwalk, CT) and thoroughly mixing the enzyme and reaction mix. PCR was performed using the PTC-200 thermal cycler (MJ Research, Inc., Watertown, MA), beginning with 40 pmol of each primer and the recommended concentrations of all other components of the kit, with the following parameters:

Step 1	94° C for 1 min (initial denaturation)
Step 2	65° C for 1 min
Step 3	68° C for 6 min
Step 4	94° C for 15 sec

Step 5	65° C for 1 min
Step 6	68° C for 7 min
Step 7	Repeat steps 4 through 6 for an additional 15 cycles
Step 8	94° C for 15 sec
Step 9	65° C for 1 min
Step 10	68° C for 7:15 min
Step 11	Repeat steps 8 through 10 for an additional 12 cycles
Step 12	72° C for 8 min
Step 13	4° C (and holding)

A 5 μl to 10 μl aliquot of the reaction mixture was analyzed by electrophoresis on a low concentration (about 0.6% to 0.8%) agarose mini-gel to determine which reactions were successful in extending the sequence. Bands thought to contain the largest products were excised from the gel, purified using QIAQUICK™ (QIAGEN Inc.), and trimmed of overhangs using Klenow enzyme to facilitate religation and cloning.

After ethanol precipitation, the products were redissolved in 13 μl of ligation buffer, 1μl T4-DNA ligase (15 units) and 1μl T4 polynucleotide kinase were added, and the mixture was incubated at room temperature for 2 to 3 hours, or overnight at 16° C. Competent E. coli cells (in 40 μl of appropriate media) were transformed with 3 μl of ligation mixture and cultured in 80 μl of SOC medium. (See, e.g., Sambrook, supra, Appendix A, p. 2.) After incubation for one hour at 37°C, the E. coli mixture was plated on Luria Bertani (LB) agar (See, e.g., Sambrook, supra, Appendix A, p. 1) containing carbenicillin (2x carb). The following day, several colonies were randomly picked from each plate and cultured in 150 μl of liquid LB/2x carb medium placed in an individual well of an appropriate commercially-available sterile 96-well microtiter plate. The following day, 5 μl of each overnight culture was transferred into a non-sterile 96-well plate and, after dilution 1:10 with water, 5 μl from each sample was transferred into a PCR array.

For PCR amplification, 18 μl of concentrated PCR reaction mix (3.3x) containing 4 units of rTth DNA polymerase, a vector primer, and one or both of the gene specific primers used for the extension reaction were added to each well. Amplification was performed using the following conditions:

Step 1	94° C for 60 sec
Step 2	94° C for 20 sec
Step 3	55° C for 30 sec
Step 4	72° C for 90 sec
Step 5	Repeat steps 2 through 4 for an additional 29 cycles
Step 6	72° C for 180 sec

Step 7 4° C (and holding)

Aliquots of the PCR reactions were run on agarose gels together with molecular weight markers. The sizes of the PCR products were compared to the original partial cDNAs, and appropriate clones were selected, ligated into plasmid, and sequenced.

The full length nucleic acid sequences of SEQ ID NO:121-158 were produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg^{2+}, $(NH_4)_2SO_4$, and β-mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100 μl PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5 μl of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure

the fluorescence of the sample and to quantify the concentration of DNA. A 5 μl to 10 μl aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending the sequence.

The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent E. coli cells. Transformed cells were selected on antibiotic-containing media, individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethysulphoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer).

In like manner, the nucleotide sequences of SEQ ID NO:80-158 are used to obtain 5' regulatory sequences using the procedure above, oligonucleotides designed for such extension, and an appropriate genomic library.

VI. Labeling and Use of Individual Hybridization Probes

Hybridization probes derived from SEQ ID NO:80-158 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-

art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250 μCi of [γ-^{32}P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10^7 counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba1, or Pvu II (DuPont NEN).

The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under increasingly stringent conditions up to 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. After XOMAT-AR film (Eastman Kodak, Rochester NY) is exposed to the blots to film for several hours, hybridization patterns are compared visually.

VII. Microarrays

A chemical coupling procedure and an ink jet device can be used to synthesize array elements on the surface of a substrate. (See, e.g., Baldeschweiler, supra.) An array analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced by hand or using available methods and machines and contain any appropriate number of elements. After hybridization, nonhybridized probes are removed and a scanner used to determine the levels and patterns of fluorescence. The degree of complementarity and the relative abundance of each probe which hybridizes to an element on the microarray may be assessed through analysis of the scanned images.

Full-length cDNAs, Expressed Sequence Tags (ESTs), or fragments thereof may comprise the elements of the microarray. Fragments suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). Full-length cDNAs, ESTs, or fragments thereof corresponding to one of the nucleotide sequences of the present invention, or selected at random from a cDNA library relevant to the present invention, are arranged on an appropriate substrate, e.g., a glass slide. The cDNA is fixed to the slide using, e.g., UV cross-linking followed by thermal

and chemical treatments and subsequent drying. (See, e.g., Schena, M. et al. (1995) Science 270:467-470; Shalon, D. et al. (1996) Genome Res. 6:639-645.) Fluorescent probes are prepared and used for hybridization to the elements on the substrate. The substrate is analyzed by procedures described above.

VIII. Complementary Polynucleotides

Sequences complementary to the HTMPN-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring HTMPN. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of HTMPN. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the HTMPN-encoding transcript.

IX. Expression of HTMPN

Expression and purification of HTMPN is achieved using bacterial or virus-based expression systems. For expression of HTMPN in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac* (*tac*) hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express HTMPN upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of HTMPN in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding HTMPN by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection

of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E. K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, HTMPN is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from HTMPN at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch 10 and 16). Purified HTMPN obtained by these methods can be used directly in the following activity assay.

X. Demonstration of HTMPN Activity

Given the chemical and structural similarity between the HTMPN and other members of the transmembrane protein families, HTMPN is identified as a new member of the membrane spanning proteins and is presumed to be involved in the regulation of cell growth. To demonstrate that increased levels of HTMPN expression correlates with decreased cell motility and increased cell proliferation, expression vectors encoding HTMPN are electroporated into highly motile cell lines, such as U-937 (ATCC CRL 1593), HEL 92.1.7 (ATCC TIB 180) and MAC10, and the motility of the electroporated and control cells are compared. Methods for the design and construction of an expression vector capable of expressing HTMPN in the desired mammalian cell line(s) chosen are well known to the art. Assays for examining the motility of cells in culture are known to the art (cf Miyake, M. et al. (1991) J. Exp. Med. 174:1347-1354 and Ikeyama, S. et al. (1993) J. Exp. Med. 177:1231-1237). Increasing the level of HTMPN in highly motile cell lines by transfection with an HTMPN expression vector inhibits or reduces the motility of these cell lines, and the amount of this inhibition is proportional to the activity of HTMPN in the assay.

Alternatively, the activity of HTMPN may be measured using an assay based upon the property of MPs to support in vitro proliferation of fibroblasts and tumor cells under serum-free conditions. (Chiquet-Ehrismann, R. et al. (1986) Cell 47:131-139.) Wells in 96 well cluster plates (Falcon, Fisher Scientific, Santa Clara, CA) are coated with HTMPN by incubation with solutions at 50-100 μg HTMPN/ml for 15 min at ambient temperature. The coating solution is aspirated, and the wells washed with Dulbecco's medium before cells are plated. Rat fibroblast cultures or rat mammary tumor cells are prepared as described. (Chiquet-Ehrismann, R. et al. supra.) and plated at a density of 10^4-10^5 cells/ml in Dulbecco's medium supplemented with 10% fetal calf serum.

After three days the medium is removed, and the cells washed three times with phosphate-buffered saline (PBS), pH 7.0, before addition of serum-free Dulbecco's medium containing 0.25 mg/ml bovine serum albumin (BSA, Fraction V, Sigma Chemical Company, St. Louis, MO). After 2 days the medium is aspirated, and 100 μl of [^{3}H]thymidine (NEN) at 2 μCi/ml in fresh Dulbecco's medium containing 0.25 mg/ml BSA is added. Parallel plates are fixed and stained to determine cell numbers. After 16 hr, the medium is aspirated, the cell layer washed with PBS, and the 10% trichloroacetic acid-precipitable radioactivity in the cell layer determined by liquid scintillation counting (normalized to relative cell numbers; Chiquet-Ehrismann, R. et al. supra). The amount of radioisotope-labeled DNA incorporated into chromatin under serum-free conditions is proportional to the activity of HTMPN.

Alternatively, HTMPN, or biologically active fragments thereof, are labeled with ^{125}I Bolton-Hunter reagent (See, e.g., Bolton et al. (1973) Biochem. J. 133:529). Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled HTMPN, washed, and any wells with labeled HTMPN complex are assayed. Data obtained using different concentrations of HTMPN are used to calculate values for the number, affinity, and association of HTMPN with the candidate molecules.

XI. Functional Assays

HTMPN function is assessed by expressing the sequences encoding HTMPN at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include pCMV SPORT (Life Technologies) and pCR3.1 (Invitrogen, Carlsbad CA), both of which contain the cytomegalovirus promoter.

5-10 μg of recombinant vector are transiently transfected into a human cell line, preferably of endothelial or hematopoietic origin, using either liposome formulations or electroporation. 1-2 μg of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP, and to evaluate properties, for example, their apoptotic state. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M. G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of HTMPN on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding HTMPN and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding HTMPN and other genes of interest can be analyzed by northern analysis or microarray techniques.

XII. Production of HTMPN Specific Antibodies

HTMPN substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) Methods Enzymol. 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard

protocols.

Alternatively, the HTMPN amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, supra, ch. 11.)

Typically, oligopeptides 15 residues in length are synthesized using an ABI 431A Peptide Synthesizer (Perkin-Elmer) using fmoc-chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, supra.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide activity by, for example, binding the peptide to plastic, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

XIII. Purification of Naturally Occurring HTMPN Using Specific Antibodies

Naturally occurring or recombinant HTMPN is substantially purified by immunoaffinity chromatography using antibodies specific for HTMPN. An immunoaffinity column is constructed by covalently coupling anti-HTMPN antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Media containing HTMPN are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of HTMPN (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/HTMPN binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and HTMPN is collected.

XIV. Identification of Molecules Which Interact with HTMPN

HTMPN, or biologically active fragments thereof, are labeled with ^{125}I Bolton-Hunter reagent (See, e.g., Bolton et al. (1973) Biochem. J. 133:529). Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled HTMPN, washed, and any wells with labeled HTMPN complex are assayed. Data

obtained using different concentrations of HTMPN are used to calculate values for the number, affinity, and association of HTMPN with the candidate molecules.

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

Table 1

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
1	80	153831	THP1PLB02	153831 (THP1PLB02), 2700741H1 (OVARTUT10), 881348R1 (THYRNOT02), 1856588F6 (PROSNOT18)
2	81	350629	LVENNOT01	350629 and 350629T6 (LVENNOT01), 3499109H1 (PROSTUT13)
3	82	729171	LUNGNOT03	729171 and 729171R6 (LUNGNOT03), 1645343H1 (HEARFET01), 680519X2 and 680519X1 (UTRSNOT02), 625051R6 (PGANNOT01), 1459466F1 (COLNFET02), 1225759T1 (COLNNOT01), 2590526H1 (LUNGNOT22), 2807811H1 (BLADTUT08)
4	83	1273641	TESTTUT02	1273641 and 1273641F6 (TESTTUT02), 1308181F6 and 1308181F1 (COLNFET02), 1427606F1 (SINTBST01), 756171H1 (BRAITUT02), 2416518F6 (HNT3AZT01), 4242346H1 (SYNWDIT01)
5	84	1427389	SINTBST01	1427389 (SINTBST01), 3097151H1 (CERVNOT03), 723779R1 (SYNOOAT01)
6	85	1458357	COLNFET02	1458357 (COLNFET02), SAOA01955F1, SAOA03146F1, SAOA03356F1, SAOA00213F1
7	86	1482837	CORPNOT02	1482837 and 1482837T6 (CORPNOT02), 869453H1 (LUNGAST01), 3564972F6 (SKINNOT05), 663983H1 (SCORNOT01), 1315073F6 (BLADTUT02), 3809242H1 (CONTTUT01), 311459T6 (LUNGNOT02), 1798893F6 (COLNNOT27)
8	87	1517434	PANCTUT01	1517434 (PANCTUT01), 2848842H1 (BRSTTUT13), 586843X1 (UTRSNOT01), 1261245R1 (SYNORAT05), 1554505F1 (BLADTUT04)
9	88	1536052	SPLNNOT04	1536052 and 1531447T6 (SPLNNOT04), 1729124T6 (BRSTTUT08)
10	89	1666118	BRSTNOT09	1666118 (BRSTNOT09), 907075R2 (COLNNOT08), 1524914T1 (UCMCL5T01), 1283459F6 (COLNNOT16)
11	90	1675560	BLADNOT05	1675560 and 1675560T6 (BLADNOT05)
12	91	1687323	PROSTUT10	1687323 and 1687323F6(PROSTUT10), 2292356R3 (BRAINON01)
13	92	1692236	PROSTUT10	1692236 (PROSTUT10), 2786557F6 (BRSTNOT13), 602869R6 and 602869T6 (BRSTTUT01), 2258230H1 (OVARTUT01), 780083T1 (MYOMNOT01), 2057230T6 (BEPINOT01), 288105R1 (EOSIHET02)
14	93	1720847	BLADNOT06	1720847, 1722250F6, and 1722250T6 (BLADNOT06)

Table 1 (cont.)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
15	94	1752821	LIVRTUT01	1752821 (LIVRTUT01), 3180328H1 (TLYJNOT01), 1969457T6 (BRSTNOT04), 2608504H1 (BONTNOT01), 2455688T6 and 2455688F6 (ENDANOT01), 1816354F6 (PROSNOT20)
16	95	1810923	PROSTUT12	1810923 and 1810923T6 (PROSTUT12), 3221260H1 (COLNNON03)
17	96	1822315	GBLATUT01	1822315 (GBLATUT01), 1841726H1 (COLNNOT07), 1598582T6 (BLADNOT03), 1264125R1 (SYNORAT05), 645048H1 (BRSTTUT02), 1474782H1 (LUNGTUT03), 352739F1 (LVENNOT01), 876001R1 (LUNGAST01)
18	97	1877777	LEUKNOT03	1877777 (LEUKNOT03), 1219656H1 (NEUTGMT01), 1471553T1 (LUNGTUT03)
19	98	1879819	LEUKNOT03	1879819 (LEUKNOT03), 1734538H1 (COLNNOT22), 1428615F6 (SINTBST01), 3558710H1 (LUNGNOT31), 1996096R6 (BRSTTUT03)
20	99	1932945	COLNNOT16	1932945 (COLNNOT16), 2383333H1 (ISLTNOT01), 2706050F6 (PONSAZT01),
21	100	2061026	OVARNOT03	2061026 (OVARNOT03)
22	101	2096687	BRAITUT02	2096687 (BRAITUT02), 2204640H1 (SPLNFET02)
23	102	2100530	BRAITUT02	2100530 (BRAITUT02), 2740969F6 (BRSTTUT14)
24	103	2357636	LUNGNOT20	2357636 (LUNGNOT20), 2693537H1 (LUNGNOT23), 1794235T6 (PROSTUT05), 235425R6 (SINTNOT02), 760091R1 (BRAITUT02), 887877R1 (PANCNOT05)
25	104	2365230	ADRENOT07	2365230 (ADRENOT07), 2921195H1 (SININOT04)
26	105	2455121	ENDANOT01	2455121 and 2455121F6 (ENDANOT01)
27	106	2472514	THP1NOT03	2472514 (THP1NOT03), 3212904H1 (BLADNOT08)
28	107	2543486	UTRSNOT11	2543486 (UTRSNOT11), 2374764H1 (ISLTNOT01), 1359576F1 (LUNGNOT12), 1357170H1 (LUNGNOT09)
29	108	2778171	OVARTUT03	2778171 (OVARTUT03), 1822045H1 (GBLATUT01), 1692535F6 (COLNNOT23), 1905275F6 (OVARNOT07)

Table 1 (cont.)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
30	109	2799575	PENCNOT01	2799575 (PENCNOT01), 874115H1 (LUNGAST01), 967837R1 (BRSTNOT05), 3235248T6 and 3235248F6 (COLNUCT03)
31	110	2804955	BLADTUT08	2804955 (BLADTUT08), 732534H1 (LUNGNOT03), 402168R1 (TMLR3DT01), 3481814H1 (KIDNNOT31), 1485989F1 (CORPNOT02)
32	111	2806395	BLADTUT08	2806395 (BLADTUT08), 1579109H1 (DUODNOT01), 1533572F1 (SPLNNOT04), 1889837F6 and 1889837T6 (BLADTUT07), 2414178F6 (HNT3AZT01)
33	112	2836858	TLYMNOT03	2836858 and 2836858CT1 (TLYMNOT03), 2127516H1 (KIDNNOT05)
34	113	2844513	DRGLNOT01	2844513 and 2844513T6 (DRGLNOT01), 388885T6 (THYMNOT02), 287344F1 (EOSIHET02), 3867626H1 (BMARNOT03)
35	114	3000380	TLYMNOT06	3000380 (TLYMNOT06), 1930658H1 (COLNTUT03), 2395295F6 (THP1AZT01), 1242456R6 (LUNGNOT03)
36	115	182532	PLACNOB01	062374H1, 062962R6, 064457R6, and 182532H1 (PLACNOB01), 3144248X12F1 (HNT2AZS07)
37	116	239589	HIPONOT01	239589H1 and 239589X13 (HIPONOT01), 264805R6 (HNT2AGT01), 552683X17 (SCORNOT01), 1595053F1 (BRAINOT14)
38	117	1671302	BMARNOT03	399804H1 (PITUNOT02), 1458549H1 (COLNFET02), 1671302F6 and 1671302H1 (BMARNOT03), 2093453R6 (PANCNOT04), 2498385F6 and 2498385T6 (ADRETUT05)
39	118	2041858	HIPONON02	063184R1 (PLACNOB01), 1294823F1 (PGANNOT03), 1303974F1 (PLACNOT02), 1648770F6 (PROSTUT09), 2041858H1 (HIPONON02)
40	119	2198863	SPLNFET02	1880470F6 (LEUKNOT03), 1888946F6 (BLADTUT07), 2198863F6 and 2198863H1 (SPLNFET02)
41	120	3250703	SEMVNOT03	1317728H1, 1318433H1, 1319354H1, 1319380F1, 1320494H1, and 1320812F1 (BLADNOT04), 3247874H1, 3249188H1, 3249385H1, and 3250703H1 (SEMVNOT03)
42	121	350287	LVENNOT01	062018F1 (PLACNOB01), 350287H1 (LVENNOT01), 869320R1 (LUNGAST01), 1416927F6 (BRAINOT12), 3083789H1 (OVARTUN01)
43	122	1618171	BRAITUT12	1618171F6 and 1618171H1 (BRAITUT12), 3316315F6 (PROSBPT03)

Table 1 (cont.)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
44	123	1625863	COLNPOT01	1625863H1 and 1625863T6 (COLNPOT01), 2100364R6 (BRAITUT02)
45	124	1638353	UTRSNOT06	1638353H1 (UTRSNOT06), 3733085H1 (SMCCNOS01), 3882774T6 (SPLNNOT11), 1626195T6 (COLNPOT01), 1495745H1 (PROSNON01)
46	125	1726843	PROSNOT14	826000T1 (PROSNOT06), 1726843F6 and 1726843H1 (PROSNOT14), 2225762F6 (SEMVNOT01), 2480248H1 (SMCANOT01), 2600692F6 (UTRSNOT10), 2728257F6 (OVARTUT05)
47	126	1754506	LIVRTUT01	907854R2 (COLNNOT09), 1354345F1 (LUNGNOT09), 1359472F1 (LUNGNOT12), 1397284F1 (BRAITUT08), 1557921F1 (BLADTUT04), 1754506F6 and 1754506H1 (LIVRTUT01)
48	127	1831378	THP1AZT01	441541R1 (MPHGNOT03), 712292R6 (SYNORAT04), 1311835F1 (COLNFET02), 1555765F6 (BLADTUT04), 1831378H1 (THP1AZT01), 1865502F6 (PROSNOT19), 3077521H1 (BONEUNT01), 3555043H1 (SYNONOT01), 3774618H1 (BRSTNOT25)
49	128	1864943	PROSNOT19	714070F1 (PROSTUT01), 736327R1 (TONSNOT01), 1864943H1 (PROSNOT19), 2672921F6 (KIDNNOT19)
50	129	1911316	CONNTUT01	777070F1 (COLNNOT05), 1911316H1 and 1911316T6 (CONNTUT01)
51	130	1943120	HIPONOT01	1516263F1 (PANCTUT01), 1943120H1 (HIPONOT01), 2469009F6 (THYRNOT08), 2522459F6 (BRAITUT21), 3202972F6 (PENCNOT02), 4383679H1 (BRAVUTT02)
52	131	2314236	NGANNOT01	2314236H1 (NGANNOT01), 2812085F6 (OVARNOT10), 3949704T6 (DRGCNOT01)
53	132	2479409	SMCANOT01	2479409F6 and 2479409H1 (SMCANOT01)
54	133	2683149	SINIUCT01	760389H1 (BRAITUT02), 1634372F6 (COLNNOT19), 1695052F6 (COLNNOT23), 1736429F6 (COLNNOT22), 2048429F6 (LIVRFET02), 2683149H1 (SINIUCT01), 3282234F6 (STOMFET02)
55	134	2774051	PANCNOT15	1852505F6 (LUNGFET03), 2774051F6 and 2774051H1 (PANCNOT15)
56	135	2869038	THYRNOT10	536017R6 (ADRENOT03), 2770632F6 (COLANOT02), 2795420F6 (NPOLNOT01), 2869038F6 and 2869038H1 (THYRNOT10), 3323992H1 (PTHYNOT03)
57	136	2918334	THYMFET03	2918334H1 (THYMFET03), SBNA01788F1

Table 1 (cont.)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
58	137	2949916	KIDNFET01	2949916H1 (KIDNFET01), SBMA00738F1
59	138	2989375	KIDNFET02	437481R6 and 437481T6 (THYRNOT01), 2989375H1 (KIDNFET02)
60	139	3316764	PROSBPT03	1328462F1 (PANCNOT07), 1691807F6 (PROSTUT10), 1851237F6 (LUNGFET03), 3316764H1 (PROSBPT03), 5092348H1 (UTRSTMR01)
61	140	3359559	PROSTUT16	943684 and 943564 (ADRENOT03), 1697079F6 (COLNNOT23), 2717735H1 (THYRNOT09), 2792705H1 (COLNTUT16), 3359559H1 (PROSTUT16)
62	141	4289208	BRABDIR01	3990421R6 (LUNGNON03), 4289208H1 (BRABDIR01)
63	142	2454013	ENDANOT01	014571R1 (THP1PLB01), 1303790T1 (PLACNOT02), 1342791T1 (COLNTUT03), 1351680F1 (LATRTUT02), 1359607T1 (LUNGNOT12), 2454013F6 and 2454013H1 (ENDANOT01)
64	143	2454048	ENDANOT01	551329R1 and 2056675R6 (BEPINOT01), 819281R1 (KERANOT02), 2454048H1 (ENDANOT01), 3143588H1 (HNT2AZS07)
65	144	2479282	SMCANOT01	873307R1 (LUNGAST01), 2479282H1 and 2479282T6 (SMCANOT01), 2610082F6 (COLNTUT15), SANA03636F1
66	145	2483432	SMCANOT01	940455T1 (ADRENOT03), 1863558T6 (PROSNOT19), 2483432H1 (SMCANOT01), 2641345H1 (LUNGTUT08), 3245089T6 (BRAINOT19), SBCA02765F1
67	146	2493824	ADRETUT05	489685F1 (HNT2AGT01), 530794H1 (BRAINOT03), 735826R1 (TONSNOT01), 2056809R6 (BEPINOT01), 2493824H1 (ADRETUT05), 2763162F6 (BRSTNOT12), 2812426H1 (OVARNOT10)
68	147	2555823	THYMNOT03	1266972F6 (BRAINOT09), 1335461T1 (COLNNOT13), 1900947F6 (BLADTUT06), 1942256T6 (HIPONOT01), 2555823H1 (THYMNOT03), SARB01019F1, SARB01303F1
69	148	2598242	OVARTUT02	320268F1 (EOSIHET02), 738915R1 (PANCNOT04), 1250161F1 (LUNGFET03), 2598242F6 and 2598242H1 (OVARTUT02), 5020793H1 (OVARNON03), SASA00178F1
70	149	2634120	COLNTUT15	1398694F1 (BRAITUT08), 1506594F1 (BRAITUT07), 2120954F6 (BRSTNOT07), 2634120F6 and 2634120H1 (COLNTUT15), 2761586H1 (BRAINOS12), 2806841F6 (BLADTUT08)

Table 1 (cont.)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
71	150	2765411	BRSTNOT12	2765236T6 and 2765411H1 (BRSTNOT12), 4058218H1 (SPLNNOT13)
72	151	2769412	COLANOT02	1715480F6 (UCMCNOT02), 2769412H1 (COLANOT02), SBDA04076F1
73	152	2842779	DRGLNOT01	1262711R1 (SYNORAT05), 1710449T6 (PROSNOT16), 2842779F6 (DRGLNOT01), 2842779H1 (DRGLNOT01), 2850941F6 (BRSTTUT13), 3123378H1 (LNODNOT05), 3457873H1 (293TF1T01), SBGA04623F1, SAOA02667F1
74	153	2966260	SCORNOT04	530242H1 (BRAINOT03), 2113607H1 (BRAITUT03), 2125619F6 (BRSTNOT07), 2155349H1 and 2156022H1 (BRAINOT09), 2966260F6, 2966260H1, and 2966260T6 (SCORNOT04), 3270731H1 (BRAINOT20), 3272328F6 (PROSBPT06)
75	154	2993326	KIDNFET02	190217F1 (SYNORAB01), 815990R1 and 815990T1 (OVARTUT01), 2993326H1 (KIDNFET02), 3629860H1 (COLNNOT38)
76	155	3001124	TLYMNOT06	2123347T6 (BRSTNOT07), 3001124H1 (TLYMNOT06), SBEA07088F3
77	156	3120070	LUNGTUT13	021565F1 (ADENINB01), 144798R1 (TLYMNOR01), 1216676H1 (BRSTTUT01), 2024357H1 (KERANOT02), 2616322H1 (GBLANOT01), 2742604H1 (BRSTTUT14), 2746025H1 (LUNGTUT11), 2924884H1 (SININOT04), 3120070H1 (LUNGTUT13)
78	157	3133035	SMCCNOT01	1478001F1 and 1482667H1 (CORPNOT02), 2812193F6 and 2812193T6 (OVARNOT10), 3133035H1 and 3133035T6 (SMCCNOT01), 5025075F6 (OVARNON03)
79	158	3436879	PENCNOT05	3323031F6 (PTHYNOT03), 3436879F6 and 3436879H1 (PENCNOT05), 4247733H1 (BRABDIT01)

Table 2

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Identification	Analytical Methods
1	240	S233 S159 T194 T43 T77 T129 T134 S171	N73 N101 N167	S33-G36 L198-L219	Somatostatin receptor tyrosine kinase	BLAST, BLOCKS, HMM
2	100	S6 S64			Meningioma-expressed antigen 11	BLAST, PRINTS, HMM
3	416	S14 S62 T109 T177 T340 S365 S380 S6 T7 T205 S327 T331 Y56	N144 N277		PMP-22/EMP/MP20 family	BLOCKS, PRINTS, HMM
4	224	T31 T57 S86 S173 S214			B cell growth factor	BLAST
5	247	S103 T60 S113 S235			5-hydroxytryptamine receptor	PRINTS
6	72				Frizzled protein	PRINTS, HMM
7	106	S97 S9 S24 T31			Dopamine 2 receptor	BLAST, PRINTS, HMM
8	239	S233	N230		PB39 protein	BLAST, HMM
9	150	S53 S111 T127			CD44 antigen precursor	PRINTS, HMM
10	110	S12	N92		Anion exchanger	BLOCKS, PRINTS, HMM
11	58		N5 N9		Neurofibromatosis type 2	BLAST, PRINTS, HMM
12	221	S35 S178 S60 S183			mitsugumin 23	BLAST, HMM

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Identification	Analytical Methods
13	262	T33 S94 S150 T225 T245 T14 S22 T30 T57 S137 T201 S207 T230	N104		C5a-anaphylatoxin receptor	PRINTS, HMM
14	90	S67 T52			Frizzled protein	PRINTS, HMM
15	208	T119 T123 T132 S56 S142	N121		Rieske iron-sulphur protein	BLOCKS, PRINTS, HMM
16	97	S61 T2			Endothelin B receptor	PRINTS, HMM
17	243	S82 T104 S168 T181 S6 S99 T195 Y24			Thromboxane receptor	PRINTS, HMM
18	162	S26	N6		G protein-couple receptor	BLOCKS, PRINTS, HMM
19	470	S285 S29 T136 S145 T167 T168 S199 S236 S249 T401 S172 S209 S254 T264 S335 T385	N118 N298 N466	R306-D308	Molluscan rhodopsin C-terminus	PRINTS, HMM
20	144	S42 S21 T72	N30 N36		Lysosome-associated membrane protein	PRINTS, HMM
21	221	S75 T82		S151-G154	Glycoprotein hormone receptor	BLAST, PRINTS, HMM
22	688	T60 T186 T103 T298 S405 S484 S488 S492 S494 S498 S499 S503 S584 S601 S611 S647 T663 T109 T188 T284 T315 S324 S347 T402 T573 S643 T658 T681 Y118	N198 N576 N577 N582	S5-G8 A80-N140	Ring3	BLAST, PRINTS

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Identification	Analytical Methods
23	439	T75 T257 S397 S424 S210 S435	N227	S365-G368	Prostanoid EP3 receptor	BLOCKS, PRINTS
24	192	S20 S44	N68		PMP-22/EMP/MP20 family	BLOCKS, PRINTS, HMM
25	175	T171 T43 S136 T7			Progesterone receptor	PRINTS
26	91	S34 S19 S29			Similar to mouse dishevelled-3(Dvl-3).	BLAST, BLOCKS, PRINTS, HMM
27	214	T34 S83 T118 T152 S17			Somatostatin receptor tyrosine kinasre	BLOCKS, PRINTS, HMM
28	250	S64 S132 T154			Sec22 homolog	BLAST, HMM
29	84	T80 T3 S76			DPM2 protein	BLAST, HMM
30	277	T140 S217 S19 S85 T129			Somatomedin B domain protein	BLOCKS, PRINTS, HMM
31	273	S64 S4 S114 S179 S256 S14 T167 T218	N187		Anion exchanger family	BLOCKS, PRINTS, HMM
32	524	T190 S5 T131 S148 S171 S262 S275 T302 S356 S404 S473 S177 S207 T492	N152 N471 N501 N513	L46-L67	G protein-coupled receptor	BLOCKS, PRINTS, HMM
33	257	S48 S52 S55 T64 S82 T90 S96 T97 S123 T129 T144 S192 S224 T227 S250	N98 N187		Nucleoporin p62 homolog	BLAST
34	274	S16 T84 S249 S56 S113	N234		Molluscan rhodopsin C-terminus	PRINTS

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Identification	Analytical Methods
35	281	S52 T150 S165 S263 T48 S116 T167 T226 T241		G125-S132 S185-G188	ABC-2 type transport protein	BLOCKS, PRINTS, HMM
36	335	S96 T113 T131 T308 T14 T146 T292 S302 S312 T317 Y258	N104 N111	E296 to A307 R127 to G129	pregnancy-specific beta 1-glycoprotein 4 precursor	Blast, BLOCKS, PRINTS, Motifs
37	280	T41 S102 T135 S148	N35 N53 N127	T56 to Y70	lysosomal membrane glycoprotein-type A precursor	Blast, BLOCKS, PRINTS, Motifs
38	210	S50 S143 S151 S63 S107 S153			Butyrophilin	Blast
39	279	T90	N66 N171		Plasma membrane glycoprotein CIG30	Blast
40	154	T75 S121 S48 S58 T112 Y84 Y90		G101 to G122 V115 to F130	Pathogenesis-related protein PR-1	Blast, BLOCKS, PRINTS
41	582	S160 S255 T256 S291 S292 S316 S351 S352 S411 S412 S471 S472 T485 S533 T559 S79 T93 S96 S151 S231		G520 to S527	semenogelin II	Blast, Motifs
42	71	S17 T45 T50		M1 to T50 P5 to C29	Integral membrane protein	BLOCKS, PRINTS
43	102	T44 S33 T75		S6 to L24 S33 to G36 I49 to I74 A2 to S29	TM4SF	BLOCKS, PRINTS, HMM
44	226	S60 T3 T4 S85 T169	N46 N82 N83	I184 to R205 G128 to Q152 Y179 to Y201	Cation-dependant mannose transporter protein	PRINTS, HMM

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Identification	Analytical Methods
45	154	T145 T148 S33 T134 T141 S152		M1 to A22 P56 to M78 P58 to M82 L91 to S110 L109 to L125	Frizzled protein	PRINTS, HMM
46	167	S154 S3 T25 T29 T126 S140		E72 to F103	GPCR	BLOCKS, PRINTS, HMM
47	545	T257 S513 S10 T11 S47 S166 S408 S495	N8 N406	E376 to K410	Human secreted protein K640 variant	Blast, BLOCKS, PRINTS, HMM
48	570	T529 S128 S130 T184 T235 T161 S293 Y199	N27 N61 N75 N87 N264	V296 to C309 F321 to F332	GPCR	Blast, BLOCKS, PRINTS,HMM
49	127	S24 T118		N10 to G30	Anion exchanger	PRINTS, HMM
50	152	T49 S16		L78 to L99 L85 to L106 V47 to Y63 Y45 to V94	TM4SF GNS1/SUR4 family	BLOCKS, HMM, Motifs
51	777	T48 S66 S162 T268 S272 T322 T355 S393 S471 S559 S574 S624 S660 S700 T742 S750 S11 T12 S196 S346 T400 S423 T493 T579 T582 S599 S723	N64 N205 N470 N706	T20 to D34 R122 to L132 L598 to L619 D331 to L349 R565 to T582	pecanex protein	Blast, PRINTS, Motifs
52	108	S52 T31 T105		L76 to Y92	GNS1/SUR4 family	BLOCKS, PRINTS, PROFILESCAN
53	66	S4 S35	N2	F22 to G58	NF2 protein	Blast, BLOCKS, PRINTS, HMM

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Identification	Analytical Methods
54	540	S135 S149 T527 T82 T94 T177 S441	N50 N92 N160 N334 N395	S115 to G118 L295 to L308 L490 to L518	LIV-1 protein	Blast, PRINTS, HMM, Motifs
55	87	T4 S13 S37 S68 S69		I46 to L82	calveolin	BLOCKS, HMM
56	100	S94		I7 to N34 G8 to F21 K65 to N91 T78 to C97	ammonium ion transporters	BLOCKS, PRINTS, HMM
57	58	T43			shox protein	BLAST, HMM
58	61	S51 S58 S42		R2 to L23	carboxyl ester lipase	Blast, PRINTS, HMM
59	50	S9		C33 to W45 C11 to L40	Lipoxygenase; growth factor and cytokines receptor family	BLOCKS, PRINTS, HMM, Motifs
60	310	T46 T156 S301 T81 S108 S166 S305		A153 to S166	C4 methyl-sterol oxidase	Blast, PRINTS, HMM
61	160	S114		L71 to W84 Y143 to T154	C5A-anaphylatoxin receptor	Blast, BLOCKS, PRINTS, HMM
62	35			K11 to M34	steroid hormone receptor	PRINTS
63	323	T92 S105 S182 T263 S301 S271	N90	M1-G31 Signal Peptide M1-A27 Signal Peptide L234-L254 TM Protein	Signal Peptide Containing Transmembrane Protein	Motifs SPScan HMM

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Identification	Analytical Methods
64	129	T112 T117 S5 S54		M1-G27 Signal Peptide M1-G27 Signal Peptide I81-V100 TM Prot.	Signal Peptide Containing Transmembrane Protein	Motifs SPScan HMM
65	461	T56 T41 S47 T56 T127 S146 S147 S197 S198 T407 S8 S47 T51 T284 T341 T407	N193 N236		Signal Peptide Containing Transmembrane Protein	Motifs
66	264	S243 T264 S33 T211 S260 S22 S243 S260	N172 N250	M1-A17 Signal Peptide M1-S22 Signal Peptide L173-Y195TM Prot. M1-L21 TM Prot. L25-R30 Prot. Splicing	Protein Splicing Protein	Motifs SPScan HMM BLOCKS
67	339	T99 S119 S157 S166 S321 T54 S55 T77 S149 S211 S279 T336 Y105	N172	M1-G30 Signal Peptide M1-G26 Signal Peptide L176-L194 TM. Prot.	Signal Peptide Containing Transmembrane Protein	Motifs SPScan HMM
68	397	S104 T148 T166 T259 S303 S317 T127 T191 S302		G202-S209 ATP/GTP binding L10-L31 Leucine zipper D106-L108 Ca binding S367-L384 Signal Peptide M1-G29 Transmembr. Prot.	Gene Regulatory Protein	Motifs SPScan BLAST HMM
69	301	T7 S52 S100 S133 S239 T155 T206	N162 N211	V12-A32 TM. Prot. V282-G300 TMr. Prot. L59-V64 aatRNA ligase	Aminoacyl tRNA ligase	Motifs HMM BLOCKS
70	217	S8 S142 T112 T197		W73-I99 TM. Prot.	Cell Proliferation Protein	Motifs HMM

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Identification	Analytical Methods
71	143	S81 T120 S139 S116		M1-C26 Signal Peptide M1-R25 Signal Peptide M1-V22 TM Prot.	Signal Peptide Containing Transmembrane Protein	Motifs SPScan HMM
72	186	T50 S132 T151 S116 Y43	N29 N104	M1-S25 Signal Peptide M1-S31 Signal Peptide F9-F28 TM Prot. A27-G891 T-cell receptor interacting molecule	T-cell Receptor Interacting Molecule	Motifs SPScan HMM BLAST
73	364	S172 S213 S243 S302	N229	L234-L255 Leucine zipper M1-G28 Signal Peptide L151-L170 TM. Prot. L72-E92 TM Prot.	Gene Regulatory Protein	Motifs SPScan HMM
74	605	S46 T54 S108 S129 S195 S220 S231 T254 T261 S316 S440 S472 S536 S560 T124	N106 N193 N395 N480	M1-A32 Signal Peptide V494-I515 TM. Prot. L17-E36 TM Prot.	2-Membrane Spanning Signal Peptide Containing Transmembrane Protein	Motifs SPScan HMM
75	97	T2 S87		M1-G26 Signal Peptide M1-G23 Signal Peptide V35-M54 TM. Prot. I11-I34 TM Prot.	2-Membrane Spanning Signal Peptide Containing Transmembrane Protein	Motifs SPScan HMM
76	247	S160 T204 S165		F72-L90 Transmembr. Prot. L45-T64 Transmembr. Prot.	2-Membrane Spanning Signal Peptide Containing Transmembrane Protein	Motifs HMM

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Identification	Analytical Methods
77	193	S60 S67		M1-D26 Signal Peptide M1-A31 Signal Peptide M80-M104 TM Prot. R109-Y129 TM Prot. S67-L108 PMP-22 Y149-Y176 PMP-22 N150-A159 Trehalase	Peripheral Myelin Protein 22	Motifs SPScan HMM BLOCKS
78	128	S30 S30 S50	N71 N84 N91	N126-L128 microbodies targeting motif	Microbody Protein	Motifs
79	115	S109		M1-S16 Signal Peptide M1-T24 Signal Peptide M1-W19 TM Prot. V27-Y46 TM Prot. V5-V15 G Prot. Receptor	G Protein Receptor	Motifs SPScan HMM PRINTS

Table 3

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease Class (Fraction of Total)	Vector
80	Reproductive (0.321) Cardiovascular (0.143) Gastrointestinal (0.134)	Cancer (0.527) Inflammation (0.232) Fetal (0.170)	pBLUESCRIPT
81	Cardiovascular (0.500) Gastrointestinal (0.250) Other (0.250)	Cancer (0.500) Fetal (0.250) Other (0.250)	pBLUESCRIPT
82	Reproductive (0.260) Cardiovascular (0.220) Gastrointestinal (0.120)	Cancer (0.500) Inflammation (0.180) Fetal (0.160)	pSPORT1
83	Nervous (0.400) Gastrointestinal (0.300) Developmental (0.100)	Cancer (0.500) Inflammation (0.300) Fetal (0.200)	pINCY1
84	Reproductive (0.266) Gastrointestinal (0.141) Cardiovascular (0.125)	Cancer (0.469) Inflammation (0.250) Fetal (0.195)	pINCY1
85	Reproductive (0.750) Developmental (0.250)	Cancer (0.750) Fetal (0.250)	pINCY1
86	Reproductive (0.250) Cardiovascular (0.143) Nervous (0.143)	Inflammation (0.321) Trauma (0.286) Cancer (0.250)	pINCY1
87	Reproductive (0.368) Developmental (0.158) Cardiovascular (0.105)	Cancer (0.421) Fetal (0.368) Inflammation (0.211)	pINCY1
88	Hematopoietic/Immune (0.417) Cardiovascular (0.250) Reproductive (0.167)	Inflammation (0.417) Cancer (0.333) Fetal (0.167)	pINCY1
89	Cardiovascular (0.220) Nervous (0.171) Reproductive (0.122)	Cancer (0.463) Inflammation (0.195) Trauma (0.171)	pINCY1
90	Gastrointestinal (0.200) Reproductive (0.200) Urologic (0.200)	Cancer (0.500) Inflammation (0.300) Other (0.100)	pINCY1

Table 3 (cont.)

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease Class (Fraction of Total)	Vector
91	Reproductive (0.306) Cardiovascular (0.204) Nervous (0.122)	Cancer (0.510) Inflammation (0.204) Fetal (0.143)	pINCY I
92	Reproductive (0.227) Hematopoietic/Immune (0.182) Cardiovascular (0.136)	Cancer (0.432) Fetal (0.273) Inflammation (0.273)	pINCY I
93	Gastrointestinal (0.375) Reproductive (0.188) Cardiovascular (0.125)	Cancer (0.500) Inflammation (0.250) Trauma (0.125)	pINCY I
94	Reproductive (0.333) Cardiovascular (0.214) Gastrointestinal (0.143)	Cancer (0.548) Inflammation (0.167) Fetal (0.143)	pINCY I
95	Cardiovascular (0.231) Gastrointestinal (0.231) Reproductive (0.192)	Cancer (0.500) Inflammation (0.231) Fetal (0.154)	pINCY I
96	Gastrointestinal (0.208) Cardiovascular (0.167) Reproductive (0.167)	Cancer (0.542) Inflammation (0.292) Other (0.083)	pINCY I
97	Hematopoietic/Immune (0.341) Reproductive (0.268) Cardiovascular (0.122)	Cancer (0.415) Inflammation (0.415) Fetal (0.195)	pINCY I
98	Gastrointestinal (0.346) Reproductive (0.231) Hematopoietic/Immune (0.154)	Inflammation (0.462) Cancer (0.385) Fetal (0.115)	pSPORT I
99	Gastrointestinal (0.400) Developmental (0.200) Nervous (0.200)	Cancer (0.400) Fetal (0.200) Neurological (0.200)	pSPORT I
100	Reproductive (0.231) Nervous (0.168) Cardiovascular (0.140)	Cancer (0.441) Inflammation (0.231) Fetal (0.133)	pSPORT I
101	Hematopoietic/Immune (0.225) Reproductive (0.225) Gastrointestinal (0.125)	Cancer (0.475) Inflammation (0.325) Fetal (0.175)	pINCY I
102	Reproductive (0.333) Gastrointestinal (0.185) Nervous (0.148)	Cancer (0.630) Fetal (0.185) Inflammation (0.111)	pINCY I

Table 3 (cont.)

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease Class (Fraction of Total)	Vector
103	Gastrointestinal (0.242) Reproductive (0.182) Developmental (0.121)	Cancer (0.455) Inflammation (0.364) Fetal (0.182)	pINCY I
104	Gastrointestinal (0.188) Hematopoietic/Immune (0.188) Urologic (0.188)	Inflammation (0.438) Cancer (0.281) Fetal (0.250)	pINCY I
105	Urologic (0.250) Cardiovascular (0.167) Gastrointestinal (0.167)	Fetal (0.500) Cancer (0.417) Inflammation (0.333)	pINCY I
106	Hematopoietic/Immune (0.333) Urologic (0.333)	Cancer (0.333) Fetal (0.333) Inflammation (0.333)	pINCY I
107	Reproductive (0.286) Cardiovascular (0.204) Nervous (0.184)	Cancer (0.592) Fetal (0.143) Inflammation (0.143)	pINCY I
108	Reproductive (0.231) Gastrointestinal (0.215) Hematopoietic/Immune (0.154)	Cancer (0.462) Inflammation (0.292) Fetal (0.185)	pINCY I
109	Reproductive (0.304) Cardiovascular (0.261) Gastrointestinal (0.130)	Cancer (0.609) Inflammation (0.174) Trauma (0.087)	pINCY I
110	Reproductive (0.256) Gastrointestinal (0.186) Hematopoietic/Immune (0.186)	Cancer (0.558) Inflammation (0.349) Trauma (0.070)	pINCY I
111	Nervous (0.200) Reproductive (0.200) Gastrointestinal (0.175)	Cancer (0.550) Fetal (0.175) Inflammation (0.150)	pINCY I
112	Developmental (0.222) Endocrine (0.222) Hematopoietic/Immune (0.222)	Cancer (0.222) Inflammation (0.222) Fetal (0.222)	pINCY I
113	Hematopoietic/Immune (0.267) Nervous (0.200) Gastrointestinal (0.133)	Cancer (0.467) Trauma (0.267) Inflammation (0.200)	pINCY I
114	Hematopoietic/Immune (0.304) Gastrointestinal (0.130) Nervous (0.130)	Inflammation (0.391) Cancer (0.304) Fetal (0.130)	pINCY I

Table 3 (cont.)

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease Class (Fraction of Total)	Vector
115	Developmental (0.333) Cardiovascular (0.167) Dermatologic (0.167)	Fetal (0.667) Inflammation (0.500)	pBLUESCRIPT
116	Nervous (0.478) Gastrointestinal (0.130) Hematopoietic/Immune (0.130)	Cancer (0.565) Fetal (0.217) Inflammation (0.217)	pBLUESCRIPT
117	Reproductive (0.222) Hematopoietic/Immune (0.200) Nervous (0.156)	Cancer (0.422) Inflammation (0.311) Fetal (0.178)	pINCY
118	Reproductive (0.256) Gastrointestinal (0.148) Nervous (0.125)	Cancer (0.430) Inflammation (0.259) Fetal (0.196)	pSPORT1
119	Reproductive (0.190) Nervous (0.167) Developmental (0.143)	Cancer (0.381) Inflammation (0.333) Fetal (0.262)	pINCY
120	Reproductive (0.800) Urologic (0.100)	Cancer (0.900) Trauma (0.100)	pINCY
121	Reproductive (0.295) Nervous (0.182) Cardiovascular (0.159)	Cancer (0.455) Inflammation (0.182) Cell Proliferation (0.159)	pBLUESCRIPT
122	Developmental (0.250) Musculoskeletal (0.250) Nervous (0.250)	Cancer (0.500) Cell Proliferation (0.250) Inflammation (0.250)	pINCY
123	Gastrointestinal (0.786) Developmental (0.071) Nervous (0.071)	Cancer (0.500) Inflammation (0.429) Cell Proliferation (0.071)	pINCY
124	Reproductive (0.348) Cardiovascular (0.159) Hematopoietic/Immune (0.130)	Cancer (0.493) Inflammation (0.246) Cell Proliferation (0.145)	pINCY
125	Nervous (0.405) Reproductive (0.324) Cardiovascular (0.108)	Cancer (0.459) Proliferation (0.189) Inflammation (0.108)	pINCY
126	Reproductive (0.275) Nervous (0.231) Gastrointestinal (0.154)	Cancer (0.549) Inflammation (0.220) Cell Proliferation (0.154)	pINCY

Table 3 (cont.)

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease Class (Fraction of Total)	Vector
127	Reproductive (0.250) Nervous (0.150) Cardiovascular (0.133)	Cancer (0.517) Cell Proliferation (0.350) Inflammation (0.233)	pINCY
128	Nervous (0.333) Reproductive (0.333) Hematopoietic/Immune (0.111)	Cancer (0.593) Inflammation (0.259) Neurological (0.111)	pINCY
129	Hematopoietic/Immune (0.304) Gastrointestinal (0.214) Reproductive (0.196)	Cancer (0.446) Inflammation (0.446) Cell Proliferation (0.161)	pINCY
130	Nervous (0.400) Reproductive (0.300) Endocrine (0.100)	Cancer (0.300) Inflammation (0.300) Cell Proliferation (0.200)	pBLUESCRIPT
131	Reproductive (0.364) Cardiovascular (0.227) Nervous (0.227)	Cancer (0.545) Inflammation (0.318) Cell Proliferation (0.091)	pSPORT1
132	Cardiovascular (0.667) Nervous (0.333)	Cell Proliferation (1.000) Cancer (0.333)	pINCY
133	Gastrointestinal (0.750) Developmental (0.125) Reproductive (0.083)	Cancer (0.375) Cell Proliferation (0.292) Inflammation (0.250)	pINCY
134	Cardiovascular (0.250) Developmental (0.250) Gastrointestinal (0.250)	Cancer (0.500) Cell Proliferation (0.500) Inflammation (0.250)	pINCY
135	Reproductive (0.250) Nervous (0.208) Endocrine (0.167)	Inflammation (0.417) Cancer (0.208) Trauma (0.167)	pINCY
136	Developmental (0.500) Reproductive (0.500)	Cancer (0.500) Cell Proliferation (0.500)	pINCY
137	Developmental (1.000)	Cell Proliferation (1.000)	pINCY
138	Developmental (0.333) Endocrine (0.333) Gastrointestinal (0.333)	Cancer (0.666) Fetal (0.333)	pINCY
139	Reproductive (0.538) Developmental (0.154) Gastrointestinal (0.154)	Cancer (0.462) Inflammation (0.231) Cell Proliferation (0.154)	pINCY

Table 3 (cont.)

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease Class (Fraction of Total)	Vector
140	Gastrointestinal (0.385) Endocrine (0.231) Reproductive (0.231)	Cancer (0.308) Inflammation (0.308) Cell Proliferation (0.077)	pINCY
141	Nervous (0.500) Cardiovascular (0.167) Gastrointestinal (0.167)	Cancer (0.333) Trauma (0.333) Neurological (0.167)	pINCY
142	Reproductive (0.220) Gastrointestinal (0.155) Nervous (0.152)	Cell Proliferation (0.637) Inflammation (0.312)	pBLUESCRIPT
143	Cardiovascular (0.202) Reproductive (0.190) Gastrointestinal (0.179)	Cell Proliferation (0.583) Inflammation (0.322)	pBLUESCRIPT
144	Reproductive (0.242) Nervous (0.158) Gastrointestinal (0.116)	Cell Proliferation (0.632) Inflammation (0.379)	pINCY
145	Cardiovascular (0.238) Reproductive (0.238) Nervous (0.143)	Cell Proliferation (0.619) Inflammation (0.476)	pINCY
146	Reproductive (0.235) Nervous (0.189) Hematopoietic/Immune (0.131)	Cell Proliferation (0.625) Inflammation (0.348)	pINCY
147	Reproductive (0.191) Hematopoietic/Immune (0.173) Nervous (0.145)	Cell Proliferation (0.582) Inflammation (0.455)	pINCY
148	Reproductive (0.279) Hematopoietic/Immune (0.140) Nervous (0.128)	Cell Proliferation (0.674) Inflammation (0.232)	pINCY
149	Reproductive (0.286) Nervous (0.214) Cardiovascular (0.095)	Cell Proliferation (0.834) Inflammation (0.215)	pINCY
150	Hematopoietic/Immune (0.400) Endocrine (0.200) Gastrointestinal (0.200)	Cell Proliferation (0.200) Inflammation (0.800)	pINCY
151	Hematopoietic/Immune (0.667) Gastrointestinal (0.167) Musculoskeletal (0.167)	Cell Proliferation (0.167) Inflammation (0.667)	pINCY

Table 3 (cont.)

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease Class (Fraction of Total)	Vector
152	Reproductive (0.240) Nervous (0.173) Hematopoietic/Immune (0.133)	Cell Proliferation (0.546) Inflammation (0.360)	pINCY
153	Reproductive (0.308) Nervous (0.231) Gastrointestinal (0.115)	Cell Proliferation (0.885) Inflammation (0.154)	pINCY
154	Nervous (0.455) Reproductive (0.182) Developmental (0.136)	Cell Proliferation (0.682) Inflammation (0.181)	pINCY
155	Reproductive (0.286) Urologic (0.286) Cardiovascular (0.143)	Cell Proliferation (0.857) Inflammation (0.429)	pINCY
156	Reproductive (0.299) Gastrointestinal (0.216) Cardiovascular (0.120)	Cell Proliferation (0.767) Inflammation (0.246)	pINCY
157	Nervous (0.222) Reproductive (0.222)	Cell Proliferation (0.333) Inflammation (0.222)	pINCY
158	Reproductive (0.429) Nervous (0.357)	Cell Proliferation (0.286) Inflammation (0.357)	pINCY

Table 4

Nucleotide SEQ ID NO:	Clone ID	Library	Library Comment
80	153831	THP1PLB02	The THP1PLB02 library was constructed by reamplification of THP1PLB01, which was made using RNA isolated from THP-1 cells cultured for 48 hours with 100 ng/ml phorbol ester (PMA), followed by a 4-hour culture in media containing 1 g/ml LPS. THP-1 (ATCC TIB 202) is a human promonocyte line derived from the peripheral blood of a 1-year-old male with acute monocytic leukemia (ref: Int. J. Cancer (1980) 26:171).
81	350629	LVENNOT01	The LVENNOT01 library was constructed using RNA isolated from the left ventricle of a 51-year-old Caucasian female, who died from an intracranial bleed.
82	729171	LUNGNOT03	The LUNGNOT03 library was constructed using polyA RNA isolated from nontumorous lung tissue of a 79-year-old Caucasian male. Tissue had been removed from the upper and lower left lobes of the lung, superior (left paratracheal) and inferior (subclavian) mediastinal lymph nodes, and the right paratracheal region. Pathology for the associated tumor tissue indicated grade 4 carcinoma. Patient history included a benign prostate neoplasm, atherosclerosis, benign hypertension, and tobacco use.
83	1273641	TESTTUT02	The TESTTUT02 library was constructed using polyA RNA isolated from a testicular tumor removed from a 31-year-old Caucasian male during unilateral orchiectomy. Pathology indicated embryonal carcinoma forming a largely necrotic mass involving the entire testicle. Rare foci of residual testicle showed intralobular germ cell neoplasia and tumor was identified at the spermatic cord margin.
84	1427389	SINTBST01	The SINTBST01 library was constructed using polyA RNA isolated from the ileum tissue of an 18-year-old Caucasian female with irritable bowel syndrome (IBS). Pathology indicated Crohn's disease of the ileum, involving 15 cm of the small bowel. Patient history included osteoporosis of the vertebra and abnormal blood chemistry. Family history included cerebrovascular disease and atherosclerotic coronary artery disease.
85	1458357	COLNFET02	The COLNFET02 library was constructed using RNA isolated from the colon tissue of a Caucasian female fetus, who died at 20 weeks' gestation from fetal demise. Serology was negative.
86	1482837	CORPNOT02	The CORPNOT02 library was constructed using polyA RNA isolated from diseased corpus callosum tissue removed from the brain of a 74-year-old Caucasian male, who died from Alzheimer's disease. Serologies were negative.

Table 4 (cont.)

Protein SEQ ID NO:	Clone ID	Library	Library Comment
87	1517434	PANCTUT01	The PANCTUT01 library was constructed using polyA RNA isolated from pancreatic tumor tissue removed from a 65-year-old Caucasian female during radical subtotal pancreatectomy. Pathology indicated an invasive grade 2 adenocarcinoma. Patient history included osteoarthritis, benign hypertension, atherosclerotic coronary artery disease, an acute myocardial infarction, benign neoplasm in the large bowel, and a cataract disorder. Family history included benign hypertension and atherosclerotic coronary artery disease, Type II diabetes, impaired renal function, and stomach cancer.
88	1536052	SPLNNOT04	The SPLNNOT04 library was constructed using polyA RNA isolated from the spleen tissue of a 2-year-old Hispanic male, who died from cerebral anoxia. Past medical history and serologies were negative.
89	1666118	BRSTNOT09	The BRSTNOT09 library was constructed using polyA RNA isolated from nontumor breast tissue removed from a 45-year-old Caucasian female during unilateral extended simple mastectomy. Pathology for the associated tumor tissue indicated invasive nuclear grade 2-3 adenocarcinoma in the same breast, with 3 of 23 lymph nodes positive for metastatic disease. There were also positive estrogen/progesterone receptors and uninvolved tissue showing proliferative changes. Patient history included valvuloplasty of mitral valve without replacement, rheumatic mitral insufficiency, rheumatic heart disease, and tobacco use. Family history included acute myocardial infarction, atherosclerotic coronary artery disease, and Type II diabetes.
90	1675560	BLADNOT05	The BLADNOT05 library was constructed using polyA RNA isolated from nontumorous bladder tissue removed from a 60-year-old Caucasian male during a radical cystectomy, prostatectomy, and vasectomy. Pathology for the associated tumor tissue indicated grade 3 transitional cell carcinoma. The patient presented with dysuria. Family history included Type I diabetes, a malignant neoplasm of the stomach, atherosclerotic coronary artery disease, and an acute myocardial infarction.
91	1687323	PROSTUT10	The PROSTUT10 library was constructed using polyA RNA isolated from prostatic tumor tissue removed from a 66-year-old Caucasian male during radical prostatectomy and regional lymph node excision. Pathology indicated an adenocarcinoma (Gleason grade 2+3). Adenofibromatous hyperplasia was also present. The patient presented with elevated prostate specific antigen (PSA). Family history included prostate cancer, secondary bone cancer, and benign hypertension.

Table 4 (cont.)

Protein SEQ ID NO:	Clone ID	Library	Library Comment
92	1692236	PROSTUT10	The PROSTUT10 library was constructed using polyA RNA isolated from prostatic tumor tissue removed from a 66-year-old Caucasian male during radical prostatectomy and regional lymph node excision. Pathology indicated an adenocarcinoma (Gleason grade 2+3). Adenofibromatous hyperplasia was also present. The patient presented with elevated prostate specific antigen (PSA). Family history included prostate cancer, secondary bone cancer, and benign hypertension.
93	1720847	BLADNOT06	The BLADNOT06 library was constructed using polyA RNA isolated from the posterior wall bladder tissue removed from a 66-year-old Caucasian male during a radical prostatectomy, radical cystectomy, and urinary diversion. Pathology for the associated tumor tissue indicated grade 3 transitional cell carcinoma. The patient presented with prostatic inflammatory disease. Family history included a malignant breast neoplasm, benign hypertension, cerebrovascular disease, atherosclerotic coronary artery disease, and lung cancer.
94	1752821	LIVRTUT01	The LIVRTUT01 library was constructed using polyA RNA isolated from liver tumor tissue removed from a 51-year-old Caucasian female during a hepatic lobectomy. Pathology indicated metastatic grade 3 adenocarcinoma consistent with colon cancer. Patient history included thrombophlebitis and pure hypercholesterolemia. Patient medications included Premarin and Provera. The patient had also received 8 cycles of fluorouracil and leucovorin in the two years prior to surgery. Family history included a malignant neoplasm of the liver.
95	1810923	PROSTUT12	The PROSTUT12 library was constructed using polyA RNA isolated from prostate tumor tissue removed from a 65-year-old Caucasian male during a radical prostatectomy. Pathology indicated an adenocarcinoma (Gleason grade 2+2). Adenofibromatous hyperplasia was also present. The patient presented with elevated prostate specific antigen (PSA).
96	1822315	GBLATUT01	The GBLATUT01 library was constructed using polyA RNA isolated from gallbladder tumor tissue removed from a 78-year-old Caucasian female during a cholecystectomy. Pathology indicated invasive grade 3 transitional cell carcinoma. The patient was taking Indural (propranolol hydrochloride) for hypertension. Family history included a cholecystectomy, atherosclerosis, hyperlipidemia, and benign hypertension.
97	1877777	LEUKNOT03	The LEUKNOT03 library was constructed using polyA RNA isolated from white blood cells of a 27-year-old female with blood type A+. The donor tested negative for cytomegalovirus (CMV).
98	1879819	LEUKNOT03	The LEUKNOT03 library was constructed using polyA RNA isolated from white blood cells of a 27-year-old female with blood type A+. The donor tested negative for cytomegalovirus (CMV).

Table 4 (cont.)

Protein SEQ ID NO:	Clone ID	Library	Library Comment
99	1932945	COLNNOT16	The COLNNOT16 library was constructed using polyA RNA isolated from nontumorous sigmoid colon tissue removed from a 62-year-old Caucasian male during a sigmoidectomy and permanent colostomy. Pathology for the associated tumor tissue indicated invasive grade 2 adenocarcinoma. Family history included benign hypertension, atherosclerotic coronary artery disease, hyperlipidemia, breast cancer, and prostate cancer.
100	2061026	OVARNOT03	The OVARNOT03 library was constructed using polyA RNA isolated from nontumorous ovarian tissue removed from a 43-year-old Caucasian female during a bilateral salpingo-oopherectomy. Pathology for the associated tumor tissue indicated grade 2 mucinous cystadenocarcinoma. Family history included atherosclerotic coronary artery disease, pancreatic cancer, stress reaction, cerebrovascular disease, breast cancer, and uterine cancer.
101	2096687	BRAITUT02	The BRAITUT02 library was constructed using polyA RNA isolated from brain tumor tissue removed from the frontal lobe of a 58-year-old Caucasian male during excision of a cerebral meningeal lesion. Pathology indicated a grade 2 metastatic hypernephroma. Patient history included a grade 2 renal cell carcinoma, insomnia, and chronic airway obstruction. Previous surgeries included a nephroureterectomy. Patient medications included Decadron (dexamethasone) and Dilantin (phenytoin). Family history included a malignant neoplasm of the kidney.
102	2100530	BRAITUT02	The BRAITUT02 library was constructed using polyA RNA isolated from brain tumor tissue removed from the frontal lobe of a 58-year-old Caucasian male during excision of a cerebral meningeal lesion. Pathology indicated a grade 2 metastatic hypernephroma. Patient history included a grade 2 renal cell carcinoma, insomnia, and chronic airway obstruction. Previous surgeries included a nephroureterectomy. Patient medications included Decadron (dexamethasone) and Dilantin (phenytoin). Family history included a malignant neoplasm of the kidney.
103	2357636	LUNGNOT20	The LUNGNOT20 library was constructed using polyA RNA isolated from lung tissue removed from the right upper lobe a 61-year-old Caucasian male during a segmental lung resection. Pathology indicated panacinal emphysema. Family history included a subdural hemorrhage, cancer at an unidentified site, benign hypertension, atherosclerotic coronary artery disease, pneumonia, and an unspecified muscle disorder.

Table 4 (cont.)

Protein SEQ ID NO:	Clone ID	Library	Library Comment
104	2365230	ADRENOT07	The ADRENOT07 library was constructed using polyA RNA isolated from adrenal tissue removed from a 61-year-old female during a bilateral adrenalectomy. Patient history included an unspecified disorder of the adrenal glands, depressive disorder, benign hypertension, vocal cord paralysis, hemiplegia, subarachnoid hemorrhage, communicating hydrocephalus, neoplasm of uncertain behavior of pituitary gland, hyperlipidemia, Type II diabetes, a benign neoplasm of the colon, osteoarthritis, Meckel's diverticulum, and tobacco use. Previous surgeries included total excision of the pituitary gland and a unilateral thyroid lobectomy. Patient medications included Calderol and Premarin (conjugated estrogen). Family history included prostate cancer, benign hypertension, myocardial infarction, atherosclerotic coronary artery disease, congestive heart failure, hyperlipidemia, depression, anxiety disorder, colon cancer, and gas gangrene.
105	2455121	ENDANOT01	The ENDANOT01 library was constructed using polyA RNA isolated from aortic endothelial cell tissue from an explanted heart removed from a male during a heart transplant.
106	2472514	THP1NOT03	The THP1NOT03 library was constructed using polyA RNA isolated from untreated THP-1 cells. THP-1 (ATCC TIB 202) is a human promonocyte line derived from the peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia (ref: Int. J. Cancer (1980) 26:171).
107	2543486	UTRSNOT11	The UTRSNOT11 library was constructed using polyA RNA isolated from uterine myometrial tissue removed from a 43-year-old female during a vaginal hysterectomy and salpingo-oopherectomy. The endometrium was in proliferative phase. Family history included benign hypertension, hyperlipidemia, colon cancer, Type II diabetes, and atherosclerotic coronary artery disease.
108	2778171	OVARTUT03	The OVARTUT03 library was constructed using polyA RNA isolated from ovarian tumor tissue removed from the left ovary of a 52-year-old mixed ethnicity female during a total abdominal hysterectomy, bilateral salpingo-oopherectomy, peritoneal and lymphatic structure biopsy, regional lymph node excision, and peritoneal tissue destruction. Pathology indicated an invasive grade 3 (of 4) seroanaplastic carcinoma. Pathology also indicated a metastatic grade 3 seroanaplastic carcinoma. Patient history included breast cancer, chronic peptic ulcer, joint pain, and a normal delivery. Family history included colon cancer, cerebrovascular disease, breast cancer, Type II diabetes, esophagus cancer, and depressive disorder.
109	2799575	PENCNOT01	The PENCNOT01 library was constructed using polyA RNA isolated from penis corpus cavernosum tissue removed from a 53-year-old male. Patient history included an untreated penile carcinoma.

Table 4 (cont.)

Protein SEQ ID NO:	Clone ID	Library	Library Comment
110	2804955	BLADTUT08	The BLADTUT08 library was constructed using polyA RNA isolated from bladder tumor tissue removed from a 72-year-old Caucasian male during a radical cystectomy and prostatectomy. Pathology indicated an invasive grade 3 (of 3) transitional cell carcinoma. Family history included myocardial infarction,cerebrovascular disease, and brain cancer.
111	2806395	BLADTUT08	The BLADTUT08 library was constructed using polyA RNA isolated from bladder tumor tissue removed from a 72-year-old Caucasian male during a radical cystectomy and prostatectomy. Pathology indicated an invasive grade 3 (of 3) transitional cell carcinoma. Family history included myocardial infarction,cerebrovascular disease, and brain cancer.
112	2836858	TLYMNOT03	The TLYMNOT03 library was constructed using polyA RNA isolated from nonactivated Th1 cells. These cells were differentiated from umbilical cord CD4 T cells with IL-12 and B7-transfected COS cells.
113	2844513	DRGLNOT01	The DRGLNOT01 library was constructed using polyA RNA isolated from dorsal root ganglion tissue removed from the low thoracic/high lumbar region of a 32-year-old Caucasian male, who died from acute pulmonary edema, acute bronchopneumonia, bilateral pleural effusions, pericardial effusion, and malignant lymphoma (natural killer cell type). Patient medications included Difulcan (fluconazole), Deltasone (prednisone), hydrocodone, Lortab, Alprazolam, Reazodone, Cytabom, Etoposide, Cisplatin, Cytarabine, and dexamethasome. The patient received radiation therapy and multiple blood transfusions.
114	3000380	TLYMNOT06	The TLYMNOT06 library was constructed using polyA RNA isolated from activated Th2 cells. These cells were differentiated from umbilical cord CD4 T cells with IL-4 in the presence of anti-IL-12 antibodies and B7-transfected COS cells, and then activated for six hours with anti-CD3 and anti-CD28 antibodies.
115	182532	PLACNOB01	The PLACNOB01 library was constructed using RNA isolated from placenta.
116	239589	HIPONOT01	The HIPONOT01 library was constructed using RNA isolated from the hippocampus tissue of a 72-year-old Caucasian female who died from an intracranial bleed. Patient history included nose cancer, hypertension, and arthritis.
117	1671302	BMARNOT03	The BMARNOT03 library was constructed using RNA isolated from the left tibial bone marrow tissue of a 16-year-old Caucasian male during a partial left tibial ostectomy with free skin graft. Patient history included an abnormality of the red blood cells. Family history included osteoarthritis.

Table 4 (cont.)

Protein SEQ ID NO:	Clone ID	Library	Library Comment
118	2041858	HIPONON02	This normalized hippocampus library was constructed from 1.13M independent clones from HIPONOT01 library. RNA was isolated from the hippocampus tissue of a 72-year-old Caucasian female who died from an intracranial bleed. Patient history included nose cancer, hypertension, and arthritis. The normalization and hybridization conditions were adapted from Soares et al. (PNAS (1994) 91:9928).
119	2198863	SPLNFET02	The SPLNFET02 library was constructed using RNA isolated from spleen tissue removed from a Caucasian male fetus, who died at 23 weeks gestation.
120	3250703	SEMVNOT03	The SEMVNOT03 library was constructed using RNA isolated from seminal vesicle tissue removed from a 56-year-old male during a radical prostatectomy. Pathology for the associated tumor tissue indicated adenocarcinoma (Gleason grade 3+3).
121	350287	LVENNOT01	The LVENNOT01 library was constructed using RNA isolated from the left ventricle of a 51-year-old Caucasian female who died from intracranial bleeding.
122	1618171	BRAITUT12	The BRAITUT12 library was constructed using RNA isolated from brain tumor tissue removed from the left frontal lobe of a 40-year-old Caucasian female during excision of a cerebral meningeal lesion. Pathology indicated grade 4 gemistocytic astrocytoma. Medications included dexamethasone and phenytoin sodium.
123	1625863	COLNPOT01	The COLNPOT01 library was constructed using RNA isolated from colon polyp tissue removed from a 40-year-old Caucasian female during a total colectomy. Pathology indicated an inflammatory pseudopolyp; this tissue was associated with a focally invasive grade 2 adenocarcinoma and multiple tubuvillous adenomas. Patient history included a benign neoplasm of the bowel. Medications included Zantac, betamethasone, furosamide, and amiodarone.
124	1638353	UTRSNOT06	The UTRSNOT06 library was constructed using RNA isolated from myometrial tissue removed from a 50-year-old Caucasian female during a vaginal hysterectomy. Pathology indicated residual atypical complex endometrial hyperplasia. Pathology for the associated tissue removed during dilation and curettage indicated fragments of atypical complex hyperplasia and a single microscopic focus suspicious for grade 1 adenocarcinoma. Patient history included benign breast neoplasm, hypothyroid disease, polypectomy, and arthralgia.

Table 4 (cont.)

Protein SEQ ID NO:	Clone ID	Library	Library Comment
125	1726843	PROSNOT14	The PROSNOT14 library was constructed using RNA isolated from diseased prostate tissue removed from a 60-year-old Caucasian male during radical prostatectomy and regional lymph node excision. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated an adenocarcinoma (Gleason grade 3+4). The patient presented with elevated prostate specific antigen (PSA). Patient history included a kidney cyst and hematuria. Family history included benign hypertension, cerebrovascular disease, and arteriosclerotic coronary artery disease.
126	1754506	LIVRTUT01	The LIVRTUT01 library was constructed using RNA isolated from liver tumor tissue removed from a 51-year-old Caucasian female during a hepatic lobectomy. Pathology indicated metastatic grade 3 adenocarcinoma consistent with colon cancer. Medications included Premarin, Provera, and earlier, fluorouracil, and leucovorin. Family history included a malignant neoplasm of the liver.
127	1831378	THP1AZT01	The THP1AZT01 library was constructed using RNA isolated from THP-1 promonocyte cells treated for 3 days with 0.8 micromolar 5-aza-2'-deoxycitidine. THP-1 (ATCC TIB 202) is a human promonocyte line derived from peripheral blood of a one-year-old Caucasian male with acute monocytic leukemia (Int. J. Cancer (1980) 26:171).
128	1864943	PROSNOT19	The PROSNOT19 library was constructed using RNA isolated from diseased prostate tissue removed from a 59-year-old Caucasian male during a radical prostatectomy with regional lymph node excision. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated an adenocarcinoma (Gleason grade 3+3). The patient presented with elevated prostate-specific antigen (PSA). Family history included benign hypertension, multiple myeloma, hyperlipidemia, and rheumatoid arthritis.
129	1911316	CONNTUT01	The CONNTUT01 library was constructed using RNA isolated from a soft tissue tumor removed from the clival area of the skull of a 30-year-old Caucasian female. Pathology indicated chondroid chordoma with neoplastic cells reactive for keratin. Medications included medroxyprogesterone acetate.
130	1943120	HIPONOT01	The HIPONOT01 library was constructed using RNA isolated from the hippocampus tissue of a 72-year-old Caucasian female who died from intracranial bleeding. Patient history included nose cancer, hypertension, and arthritis.
131	2314236	NGANNOT01	The NGANNOT01 library was constructed using RNA isolated from tumorous neuroganglion tissue removed from a 9-year-old Caucasian male during a soft tissue excision of the chest wall. Pathology indicated a ganglioneuroma forming an encapsulated lobulated mass. The tissue from the medial aspect pleura surrounding the tumor showed fibrotic tissue with chronic inflammation. Family history included asthma.

Table 4 (cont.)

Protein SEQ ID NO:	Clone ID	Library	Library Comment
132	2479409	SMCANOT01	The SMCANOT01 library was constructed using RNA isolated from an aortic smooth muscle cell line derived from the explanted heart of a male during a heart transplant.
133	2683149	SINIUCT01	The SINIUCT01 library was constructed using RNA isolated from ileum tissue obtained from a 42-year-old Caucasian male during a total intra-abdominal colectomy and endoscopic jejunostomy. Previous surgeries included polypectomy, colonoscopy, and spinal canal exploration. Medications included Prednisone, mesalamine, and Deltasone. Family history included cerebrovascular disease, benign hypertension, atherosclerotic coronary artery disease, and type II diabetes.
134	2774051	PANCNOT15	The PANCNOT15 library was constructed using RNA isolated from diseased pancreatic tissue removed from a 15-year-old Caucasian male during an exploratory laparotomy with distal pancreatectomy and total splenectomy. Pathology indicated islet cell hyperplasia. A single pancreatic lymph node was negative. Family history included prostate cancer and cardiovacular disease.
135	2869038	THYRNOT10	The THYRNOT10 library was constructed using RNA isolated from the diseased left thyroid tissue removed from a 30-year-old Caucasian female during a unilateral thyroid lobectomy and parathyroid reimplantation. Pathology indicated lymphocytic thyroiditis. Pathology for the associated tumor indicated grade 1 (of 4) papillary carcinoma of the right thyroid gland, follicular variant. Multiple perithyroidal and other lymph nodes were negative. Patient history included hyperlipidemia and benign ovary neoplasm. Medications included Premarian, Provera, and Anaprox.
136	2918334	THYMFET03	The THYMFET03 library was constructed using RNA isolated from thymus tissue removed from a Caucasian male fetus who died at premature birth. Serology was negative.
137	2949916	KIDNFET01	The KIDNFET01 library was constructed using RNA isolated from kidney tissue removed from a Caucasian female fetus, who died at 17 weeks gestation from anencephalus. Serology was negative.
138	2989375	KIDNFET02	The KIDNFET02 library was constructed using RNA isolated from kidney tissue removed from a Caucasian male fetus who was stillborn with a hypoplastic left heart at 23 weeks gestation. Serology was negative.

Table 4 (cont.)

Protein SEQ ID NO:	Clone ID	Library	Library Comment
139	3316764	PROSBPT03	The PROSBPT03 library was constructed using RNA isolated from diseased prostate tissue removed from a 59-year-old Caucasian male during a radical prostatectomy and regional lymph node excision. Pathology indicated benign prostatic hyperplasia. Pathology for the associated tumor indicated adenocarcinoma, Gleason grade 3+3. The patient presented with elevated prostate specific antigen (PSA), benign hypertension, and hyperlipidemia. Medications included Lotensin and Pravachol. Family history included cerebrovascular disease, benign hypertension, and prostate cancer.
140	3359559	PROSTUT16	The PROSTUT16 library was constructed using RNA isolated from prostate tumor tissue removed from a 55-year-old Caucasian male. Pathology indicated adenocarcinoma, Gleason grade 5+4. Adenofibromatous hyperplasia was also present. The patient presented with elevated prostate specific antigen (PSA). Patient history included calculus of the kidney. Family history included lung cancer and breast cancer.
141	4289208	BRABDIR01	The BRABDIR01 library was constructed using RNA isolated from diseased cerebellum tissue removed from the brain of a 57-year-old Caucasian male who died from a cerebrovascular accident. Patient history included Huntington's disease, emphysema, and long-term tobacco use.
142	2454013	ENDANOT01	The ENDANOT01 library was constructed using RNA isolated from aortic endothelial cell tissue from an explanted heart removed from a male during a heart transplant.
143	2454048	ENDANOT01	The ENDANOT01 library was constructed using RNA isolated from aortic endothelial cell tissue from an explanted heart removed from a male during a heart transplant.
144	2479282	SMCANOT01	The SMCANOT01 library was constructed using RNA isolated from an aortic smooth muscle cell line derived from the explanted heart of a male during a heart transplant.
145	2483432	SMCANOT01	The SMCANOT01 library was constructed using RNA isolated from an aortic smooth muscle cell line derived from the explanted heart of a male during a heart transplant.
146	2493824	ADRETUT05	The ADRETUT05 library was constructed using RNA isolated from adrenal tumor tissue removed from a 52-year-old Caucasian female during a unilateral adrenalectomy. Pathology indicated a pheochromocytoma.

Table 4 (cont.)

Protein SEQ ID NO:	Clone ID	Library	Library Comment
147	2555823	THYMNOT03	The THYMNOT03 library was constructed using 0.5 micrograms of polyA RNA isolated from thymus tissue removed from a 21-year-old Caucasian male during a thymectomy. Pathology indicated an unremarkable thymus and a benign parathyroid adenoma in the right inferior parathyroid. Patient history included atopic dermatitis, a benign neoplasm of the parathyroid, and tobacco use. Patient medications included multivitamins. Family history included atherosclerotic coronary artery disease and benign hypertension.
148	2598242	OVARTUT02	The OVARTUT02 library was constructed using RNA isolated from ovarian tumor tissue removed from a 51-year-old Caucasian female during an exploratory laparotomy, total abdominal hysterectomy, salpingo-oophorectomy, and an incidental appendectomy. Pathology indicated mucinous cystadenoma presenting as a multiloculated neoplasm involving the entire left ovary. The right ovary contained a follicular cyst and a hemorrhagic corpus luteum. The uterus showed proliferative endometrium and a single intramural leiomyoma. The peritoneal biopsy indicated benign glandular inclusions consistent with endosalpingiosis. Family history included atherosclerotic coronary artery disease, benign hypertension, breast cancer, and uterine cancer.
149	2634120	COLNTUT15	The COLNTUT15 library was constructed using RNA isolated from colon tumor tissue obtained from a 64-year-old Caucasian female during a right hemicolectomy with ileostomy and bilateral salpingo-oophorectomy (removal of the fallopian tubes and ovaries). Pathology indicated an invasive grade 3 adenocarcinoma. Patient history included hypothyroidism, depression, and anemia. Family history included colon cancer and uterine cancer.
150	2765411	BRSTNOT12	The BRSTNOT12 library was constructed using RNA isolated from diseased breast tissue removed from a 32-year-old Caucasian female during a bilateral reduction mammoplasty. Pathology indicated nonproliferative fibrocystic disease. Family history included benign hypertension and atherosclerotic coronary artery disease.
151	2769412	COLANOT02	The COLANOT02 library was constructed using RNA isolated from diseased ascending colon tissue removed from a 25-year-old Caucasian female during a multiple segmental resection of the large bowel. Pathology indicated moderately to severely active chronic ulcerative colitis, involving the entire colectomy specimen and sparing 2 cm of the attached ileum. Grossly, the specimen showed continuous involvement from the rectum proximally; marked mucosal atrophy and no skip areas were identified. Microscopically, the specimen showed dense, predominantly mucosal inflammation and crypt abscesses. Patient history included benign large bowel neoplasm.

Table 4 (cont.)

Protein SEQ ID NO:	Clone ID	Library	Library Comment
152	2842779	DRGLNOT01	The DRGLNOT01 library was constructed using RNA isolated from dorsal root ganglion tissue removed from the low thoracic/high lumbar region of a 32-year- old Caucasian male who died from acute pulmonary edema and bronchopneumonia, bilateral pleural and pericardial effusions, and malignant lymphoma (natural killer cell type). Patient history included probable cytomegalovirus, infection, hepatic congestion and steatosis, splenomegaly, hemorrhagic cystitis, thyroid hemorrhage, and Bell's palsy.
153	2966260	SCORNOT04	The SCORNOT04 library was constructed using RNA isolated from cervical spinal cord tissue removed from a 32-year-old Caucasian male who died from acute pulmonary edema and bronchopneumonia, bilateral pleural and pericardial effusions, and malignant lymphoma (natural killer cell type). Patient history included probable cytomegalovirus, infection, hepatic congestion and steatosis, splenomegaly, hemorrhagic cystitis, thyroid hemorrhage, and Bell's palsy.
154	2993326	KIDNFET02	The KIDNFET02 library was constructed using RNA isolated from kidney tissue removed from a Caucasian male fetus, who was stillborn with a hypoplastic left heart and died at 23 weeks' gestation.
155	3001124	TLYMNOT06	The TLYMNOT06 library was constructed using 0.5 micrograms of polyA RNA isolated from activated Th2 cells. These cells were differentiated from umbilical cord CD4 T cells with IL-4 in the presence of anti-IL-12 antibodies and B7-transfected COS cells, and then activated for six hours with anti-CD3 and anti-CD28 antibodies.
156	3120070	LUNGTUT13	The LUNGTUT13 library was constructed using RNA isolated from tumorous lung tissue removed from the right upper lobe of a 47-year-old Caucasian male during a segmental lung resection. Pathology indicated invasive grade 3 (of 4) adenocarcinoma. Family history included atherosclerotic coronary artery disease, and type II diabetes.
157	3133035	SMCCNOT01	The SMCCNOT01 library was constructed using RNA isolated from smooth muscle cells removed from the coronary artery of a 3-year-old Caucasian male.
158	3436879	PENCNOT05	The PENCNOT05 library was constructed using RNA isolated from penis left corpus cavernosum tissue.

Table 5

Program	Description	Reference	Parameter Threshold
ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%
ABI AutoAssembler	A program that assembles nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25: 3389-3402.	*ESTs:* Probability value= 1.0E-8 or less *Full Length sequences*: Probability value= 1.0E-10 or less
FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises as least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad Sci. 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183: 63-98; and Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489.	*ESTs:* fasta E value=1.06E-6 *Assembled ESTs*: fasta Identity= 95% or greater and Match length=200 bases or greater; fastx E value=1.0E-8 or less *Full Length sequences:* fastx score=100 or greater
BLIMPS	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS and PRINTS databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S and J.G. Henikoff, Nucl. Acid Res., 19:6565-72, 1991. J.G. Henikoff and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37: 417-424.	Score=1000 or greater; Ratio of Score/Strength = 0.75 or larger; and Probability value= 1.0E-3 or less
PFAM	A Hidden Markov Models-based application useful for protein family search.	Krogh, A. et al. (1994) J. Mol. Biol., 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322.	Score=10-50 bits, depending on individual protein families

Table 5 cont.

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25: 217-221.	Score= 4.0 or greater
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M. S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score= 120 or greater; Match length= 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12: 431-439.	Score=5 or greater
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch et al. supra; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

What is claimed is:

1. A substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14; SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, and SEQ ID NO:79 and fragments thereof.

2. A substantially purified variant having at least 90% amino acid sequence identity to the amino acid sequence of claim 1.

3. An isolated and purified polynucleotide encoding the polypeptide of claim 1.

4. An isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide of claim 3.

5. An isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide of claim 3.

6. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 3.

7. A method for detecting a polynucleotide, the method comprising the steps of:

(a) hybridizing the polynucleotide of claim 6 to at least one nucleic acid

in a sample, thereby forming a hybridization complex; and

(b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of the polynucleotide in the sample.

8. The method of claim 7 further comprising amplifying the polynucleotide prior to hybridization.

9. An isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:134, SEQ ID NO:135, SEQ ID NO:136, SEQ ID NO:137, SEQ ID NO:138, SEQ ID NO:139, SEQ ID NO:140, SEQ ID NO:141, SEQ ID NO:142, SEQ ID NO:143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:154, SEQ ID NO:155, SEQ ID NO:156, SEQ ID NO:157, and SEQ ID NO:158 and fragments thereof.

10. An isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide of claim 9.

11. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 9.

12. An expression vector comprising at least a fragment of the polynucleotide of claim 3.

13. A host cell comprising the expression vector of claim 12.

14. A method for producing a polypeptide, the method comprising the steps of:

a) culturing the host cell of claim 13 under conditions suitable for the expression of the polypeptide; and

b) recovering the polypeptide from the host cell culture.

15. A pharmaceutical composition comprising the polypeptide of claim 1 in conjunction with a suitable pharmaceutical carrier.

16. A purified antibody which specifically binds to the polypeptide of claim 1.

17. A purified agonist of the polypeptide of claim 1.

18. A purified antagonist of the polypeptide of claim 1.

19. A method for treating or preventing a disorder associated with decreased expression or activity of HTMPN, the method comprising administering to a subject in need of such treatment an effective amount of the pharmaceutical composition of claim 15.

20. A method for treating or preventing a disorder associated with increased expression or activity of HTMPN, the method comprising administering to a subject in need of such treatment an effective amount of the antagonist of claim 18.

SEQUENCE LISTING

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KASER, Matthew R.
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AU-YOUNG, Janice

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<130> PF-0526 PCT

<140> To Be Assigned
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<151> 1998-05-29; 1998-07-02; 1998-10-02; 1998-11-24

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170 175 180
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35 40 45
Val Cys Pro His Phe Met Gly Leu Leu Leu Gly Leu Leu Leu Leu
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His Gln Leu Lys Arg Leu Glu Glu His Arg Tyr Gln Ser Ala Gly
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Arg Ser Leu Leu Glu Pro Leu Val Gln Gly Tyr Trp Glu Trp Leu
65 70 75
Val Arg Arg Val Pro Ser Trp Ile Ala Pro Asn Leu Ile Thr Ile
80 85 90
Ile Gly Leu Ser Ile Asn Ile Cys Thr Thr Ile Leu Leu Val Phe
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Tyr Cys Pro Thr Ala Thr Glu Gln Ala Pro Leu Trp Ala Tyr Ile
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125 130 135
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140 145 150
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Val Leu Gly Thr Cys Ile Ala Val Gln Leu Gly Thr Asn Pro Asp
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185 190 195
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215 220 225
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230 235 240
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245 250 255
Ala Gly Thr Ile Phe Pro Val Thr Asn Tyr Phe Arg Val Ile Phe
260 265 270
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290 295 300
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Gln Tyr Phe Asn Ser Phe Ile Asp Glu Tyr Ile Val Leu Trp Ile
365 370 375
Ala Leu Val Phe Ser Phe Phe Asp Leu Ile Arg Tyr Cys Val Ser
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Cys Cys Cys Pro Cys Cys Gln Arg Leu Leu Leu Thr Arg Lys Lys
50 55 60
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65 70 75
Ile Thr Leu Thr Trp Trp Ala Leu Phe Ser Ser Pro Thr Glu Ser
80 85 90
Tyr Asp Pro Ala Asp Ile Ser Glu Gly Ser Thr Ala Leu Trp Ile
95 100 105
Asn Thr Phe Leu Gly Val Ser Thr Leu Leu Ala Leu Trp Thr Leu
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125 130 135
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140 145 150
Ala Leu Gln Pro Ser Ile Phe Ser Val Leu Ala Asn Gly Gly Gln
155 160 165
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170 175 180
Met Asn Cys His Leu Leu Ile Leu Glu Thr Phe Leu Met Thr Val
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                65                  70                  75
Ala Ala Val Ser Val Leu Leu Gln Glu Val Phe Arg Phe Ala Tyr
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Tyr Lys Leu Leu Lys Lys Ala Asp Glu Gly Leu Ala Ser Leu Ser
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Glu Asp Gly Arg Ser Pro Ile Ser Ile Arg Gln Met Ala Tyr Val
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Gly Asp Ser Pro Tyr Tyr Phe Leu Thr Ser Ala Phe Leu Thr Ala
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Ser His Leu Leu Thr Ser Gly Leu Thr Phe Leu Asn Pro Trp Tyr
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35 40 45
Ile Lys Leu Phe His Arg Thr Ser Trp Pro Pro His Ser His Ala
50 55 60
Leu Pro Thr Gln Pro Gly Pro Leu Pro Ala Pro Phe Ile Lys Ala
65 70 75
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Leu Thr Ala Pro Val Ile Gly Tyr Ile Met Asp Trp Arg Leu Lys
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Gln Gly Glu Lys Lys Lys Lys Lys Arg Asp Arg Gln Ile Gln Lys
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Phe Gly Ser Leu Thr Gly Leu Gln Ser Leu Ile Ser Ala Leu Phe
155 160 165
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170 175 180
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Ser Gln Ser Thr Ala Phe Leu Thr Met Cys Gly Val Thr Tyr Ala
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Trp Tyr Met Pro Leu Leu Leu Leu Lys Phe Tyr Ser Leu Leu Leu
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50 55 60
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Ala Tyr Ser Ala Val Pro Val Arg His Phe Ala Thr Lys Lys Ala
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Lys Ala Lys Gly Lys Gly Gln Ser Gln Thr Arg Val Asn Ile Asn
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Val Val Thr Ala Asp Gly Lys Leu Ala Leu Asn Gln Ile Ser Gln
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Ile Ser Met Lys Ser Pro Gln Leu Ile Leu Val Asn Met Ala Ser
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Phe Pro Glu Cys Thr Ala Ala Ala Ile Lys Ala Ile Arg Glu Ser
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Gly Met Asn Leu Asn Pro Glu Val Glu Gly Thr Leu Ile Arg Val
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Pro Ile Pro Gln Val Thr Arg Glu His Arg Glu Met Leu Val Lys
185 190 195
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200 205 210
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215 220 225
Val Ser Glu Asp Thr Ile Arg Leu Ile Glu Lys Gln Ile Ser Gln
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35 40 45
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35 40 45
Asp Ser Ser Ser Gly Pro Gln Arg Leu Val Ser Phe Arg Leu Ile
50 55 60
Arg Asp Leu His Gln His Leu Arg Glu Arg Asp Ser Lys Leu Tyr
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Leu His Glu Leu Leu Glu Gly Ser Glu Ile Tyr Leu Pro Glu Val
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35 40 45
Arg Arg Ser Leu Glu Lys Glu Lys Asn Ser Leu Met Asn Lys Ala
50 55 60

Ser Asn Tyr Glu Lys Glu Leu Lys Phe Leu Arg Gln Glu Asn Arg
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Ala Leu Leu Tyr Met Ile Glu Asn Gly Pro Gly Glu Ile Pro Val
50 55 60
Asp Phe Ser Lys Gln Tyr Ser Ala Ser Trp Met Cys Leu Ser Leu
65 70 75
Leu Ala Ala Leu Ala Cys Ser Ala Gly Asp Thr Trp Ala Ser Glu
80 85 90
Val Gly Pro Val Leu Ser Lys Ser Ser Pro Arg Leu Ile Thr Thr
95 100 105
Trp Glu Lys Val Pro Val Gly Thr Asn Gly Gly Val Thr Val Val
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Gly Leu Val Ser Ser Leu Leu Gly Gly Thr Phe Val Gly Ile Ala
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Tyr Phe Leu Thr Gln Leu Ile Phe Val Asn Asp Leu Asp Ile Ser
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155 160 165
Leu Gly Ser Ile Val Asp Ser Tyr Leu Gly Ala Thr Met Gln Tyr
170 175 180
Thr Gly Leu Asp Glu Ser Thr Gly Met Val Val Asn Ser Pro Thr
185 190 195
Asn Lys Ala Arg His Ile Ala Gly Lys Pro Ile Leu Asp Asn Asn
200 205 210
Ala Trp Ile Cys Phe Leu Leu Phe Leu Leu Pro Ser Cys Ser Gln
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 1               5                  10                  15
Leu Leu Leu Ser Tyr Asp Leu Phe Val Asn Ser Phe Ser Glu Leu
                20                  25                  30
Leu Gln Lys Thr Pro Val Ile Gln Leu Val Leu Phe Ile Ile Gln
                35                  40                  45
Asp Ile Ala Val Leu Phe Asn Ile Ile Ile Ile Phe Leu Met Phe
                50                  55                  60
Phe Asn Thr Phe Val Phe Gln Ala Gly Leu Val Asn Leu Leu Phe
                65                  70                  75
His Lys Phe Lys Gly Thr Ile Ile Leu Thr Ala Val Tyr Phe Ala
                80                  85                  90
Leu Ser Ile Ser Leu His Val Trp Val Met Asn Leu Arg Trp Lys
                95                 100                 105
Asn Ser Asn Ser Phe Ile Trp Thr Asp Gly Leu Gln Met Leu Phe
               110                 115                 120
Val Phe Gln Arg Leu Ala Ala Val Leu Tyr Cys Tyr Phe Tyr Lys
               125                 130                 135
Arg Thr Ala Val Arg Leu Gly Asp Pro His Phe Tyr Gln Asp Ser
               140                 145                 150
Leu Trp Leu Arg Lys Glu Phe Met Gln Val Arg Arg
               155                 160
```

<210> 19
<211> 470
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 1879819

<400> 19
```
Met Leu Ser Pro Ser Pro Gly Lys Gly Pro Pro Pro Ala Val Ala
 1               5                  10                  15
Pro Arg Pro Lys Ala Pro Leu Gln Leu Gly Pro Ser Ser Ser Ile
                20                  25                  30
Lys Glu Lys Gln Gly Pro Leu Leu Asp Leu Phe Gly Gln Lys Leu
                35                  40                  45
Pro Ile Ala His Thr Pro Pro Pro Pro Pro Ala Pro Pro Leu Pro
                50                  55                  60
Leu Pro Glu Asp Pro Gly Thr Leu Ser Ala Glu Arg Arg Cys Leu
                65                  70                  75
Thr Gln Pro Val Glu Asp Gln Gly Val Ser Thr Gln Leu Leu Ala
```

80 85 90
Pro Ser Gly Ser Val Cys Phe Ser Tyr Thr Gly Thr Pro Trp Lys
95 100 105
Leu Phe Leu Arg Lys Glu Val Phe Tyr Pro Arg Glu Asn Phe Ser
110 115 120
His Pro Tyr Tyr Leu Arg Leu Leu Cys Glu Gln Ile Leu Arg Asp
125 130 135
Thr Phe Ser Glu Ser Cys Ile Arg Ile Ser Gln Asn Glu Arg Arg
140 145 150
Lys Met Lys Asp Leu Leu Gly Gly Leu Glu Val Asp Leu Asp Ser
155 160 165
Leu Thr Thr Thr Glu Asp Ser Val Lys Lys Arg Ile Val Val Ala
170 175 180
Ala Arg Asp Asn Trp Ala Asn Tyr Phe Ser Arg Phe Phe Pro Val
185 190 195
Ser Gly Glu Ser Gly Ser Asp Val Gln Leu Leu Ala Val Ser His
200 205 210
Arg Gly Leu Arg Leu Leu Lys Val Thr Gln Gly Pro Gly Leu Arg
215 220 225
Pro Asp Gln Leu Lys Ile Leu Cys Ser Tyr Ser Phe Ala Glu Val
230 235 240
Leu Gly Val Glu Cys Arg Gly Gly Ser Thr Leu Glu Leu Ser Leu
245 250 255
Lys Ser Glu Gln Leu Val Leu His Thr Ala Arg Ala Arg Ala Ile
260 265 270
Glu Ala Leu Val Glu Leu Phe Leu Asn Glu Leu Lys Lys Asp Ser
275 280 285
Gly Tyr Val Ile Ala Leu Arg Ser Tyr Ile Thr Asp Asn Cys Ser
290 295 300
Leu Leu Ser Phe His Arg Gly Asp Leu Ile Lys Leu Leu Pro Val
305 310 315
Cys His Pro Gly Ala Arg Leu Ala Val Trp Leu Cys Arg Gly Pro
320 325 330
Phe Arg Thr Leu Ser Cys Arg His Ser Ala Ala Gly Cys Arg Ser
335 340 345
Arg Leu Phe Leu Leu Gln Gly Ala Glu Glu Trp Leu Ala Gln Gly
350 355 360
Ser Ala Val Gln Arg Gly Thr Arg Ala Gly Ser Val Gly Gln Gly
365 370 375
Leu Arg Gly Glu Glu Asp Gly Arg Gly Thr Ser Arg Gly Lys Ala
380 385 390
Cys Leu Arg Leu Arg Lys Glu Arg Gly Leu Thr Thr Pro Glu Ala
395 400 405
Ala Met Arg Trp Asp His Pro Ala Val Arg Leu Leu Trp Leu Pro
410 415 420
Leu Cys Pro Leu Leu Met Ala Arg Leu Val Ser Pro Ala Arg Leu
425 430 435
Cys Thr Pro Cys Arg Gln Gly Leu Gly Trp Met Leu Leu Leu Cys
440 445 450
Pro Thr Trp Tyr Leu Val Gln Gly Cys Pro Ser Arg Cys Leu Ile
455 460 465
Asn Ser Ser Ser Leu
470

<210> 20
<211> 144

<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 1932945

<400> 20
Met Glu Arg Glu Gly Ser Gly Gly Ser Gly Gly Ser Ala Gly Leu
1 5 10 15
Leu Gln Gln Ile Leu Ser Leu Lys Val Val Pro Arg Val Gly Asn
20 25 30
Gly Thr Leu Cys Pro Asn Ser Thr Ser Leu Cys Ser Phe Pro Glu
35 40 45
Met Trp Tyr Gly Val Phe Leu Trp Ala Leu Val Ser Ser Leu Phe
50 55 60
Phe His Val Pro Ala Gly Leu Leu Ala Leu Phe Thr Leu Arg His
65 70 75
His Lys Tyr Gly Arg Phe Met Ser Val Ser Ile Leu Leu Met Gly
80 85 90
Ile Val Gly Pro Ile Thr Ala Gly Ile Leu Thr Ser Ala Ala Ile
95 100 105
Ala Gly Val Tyr Arg Ala Ala Gly Lys Glu Met Ile Pro Phe Glu
110 115 120
Ala Leu Thr Leu Gly Thr Gly Gln Thr Phe Cys Val Leu Val Val
125 130 135
Ser Phe Leu Arg Ile Leu Ala Thr Leu
140

<210> 21
<211> 221
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2061026

<400> 21
Met Ala Leu Ala Leu Ala Ala Leu Ala Ala Val Glu Pro Ala Cys
1 5 10 15
Gly Ser Arg Tyr Gln Gln Leu Gln Asn Glu Glu Glu Ser Gly Glu
20 25 30
Pro Glu Gln Ala Ala Gly Asp Ala Pro Pro Pro Tyr Ser Ser Ile
35 40 45
Ser Ala Glu Ser Ala Ala Tyr Phe Asp Tyr Lys Asp Glu Ser Gly
50 55 60
Phe Pro Lys Pro Pro Ser Tyr Asn Val Ala Thr Thr Leu Pro Ser
65 70 75
Tyr Asp Glu Ala Glu Arg Thr Lys Ala Glu Ala Thr Ile Pro Leu
80 85 90
Val Pro Gly Arg Asp Glu Asp Phe Val Gly Arg Asp Asp Phe Asp
95 100 105
Asp Ala Asp Gln Leu Arg Ile Gly Asn Asp Gly Ile Phe Met Leu

110 115 120
Thr Phe Phe Met Ala Phe Leu Phe Asn Trp Ile Gly Phe Phe Leu
125 130 135
Ser Phe Cys Leu Thr Thr Ser Ala Ala Gly Arg Tyr Gly Ala Ile
140 145 150
Ser Gly Phe Gly Leu Ser Leu Ile Lys Trp Ile Leu Ile Val Arg
155 160 165
Phe Ser Thr Tyr Phe Pro Gly Tyr Phe Asp Gly Gln Tyr Trp Leu
170 175 180
Trp Trp Val Phe Leu Val Leu Gly Phe Leu Leu Phe Leu Arg Gly
185 190 195
Phe Ile Asn Tyr Ala Lys Val Arg Lys Met Pro Glu Thr Phe Ser
200 205 210
Asn Leu Pro Arg Thr Arg Val Leu Phe Ile Tyr
215 220

<210> 22
<211> 688
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2096687

<400> 22
Met Ser Ala Glu Ser Gly Pro Gly Thr Arg Leu Arg Asn Leu Pro
1 5 10 15
Val Met Gly Asp Gly Leu Glu Thr Ser Gln Met Ser Thr Thr Gln
20 25 30
Ala Gln Ala Gln Pro Gln Pro Ala Asn Ala Ala Ser Thr Asn Pro
35 40 45
Pro Pro Pro Glu Thr Ser Asn Pro Asn Lys Pro Lys Arg Gln Thr
50 55 60
Asn Gln Leu Gln Tyr Leu Leu Arg Val Val Leu Lys Thr Leu Trp
65 70 75
Lys His Gln Phe Ala Trp Pro Phe Gln Gln Pro Val Asp Ala Val
80 85 90
Lys Leu Asn Leu Pro Asp Tyr Tyr Lys Ile Ile Lys Thr Pro Met
95 100 105
Asp Met Gly Thr Ile Lys Lys Arg Leu Glu Asn Asn Tyr Tyr Trp
110 115 120
Asn Ala Gln Glu Cys Ile Gln Asp Phe Asn Thr Met Phe Thr Asn
125 130 135
Cys Tyr Ile Tyr Asn Lys Pro Gly Asp Asp Ile Val Leu Met Ala
140 145 150
Glu Ala Leu Glu Lys Leu Phe Leu Gln Lys Ile Asn Glu Leu Pro
155 160 165
Thr Glu Glu Thr Glu Ile Met Ile Val Gln Ala Lys Gly Arg Gly
170 175 180
Arg Gly Arg Lys Glu Thr Gly Thr Ala Lys Pro Gly Val Ser Thr
185 190 195
Val Pro Asn Thr Thr Gln Ala Ser Thr Pro Pro Gln Thr Gln Thr

```
                200                 205                 210
Pro Gln Pro Asn Pro Pro Pro Val Gln Ala Thr Pro His Pro Phe
                215                 220                 225
Pro Ala Val Thr Pro Asp Leu Ile Val Gln Thr Pro Val Met Thr
                230                 235                 240
Val Val Pro Pro Gln Pro Leu Gln Thr Pro Pro Pro Val Pro Pro
                245                 250                 255
Gln Pro Gln Pro Pro Pro Ala Pro Ala Pro Gln Pro Val Gln Ser
                260                 265                 270
His Pro Pro Ile Ile Ala Ala Thr Pro Gln Pro Val Lys Thr Lys
                275                 280                 285
Lys Gly Val Lys Arg Lys Ala Asp Thr Thr Thr Pro Thr Thr Ile
                290                 295                 300
Asp Pro Ile His Glu Pro Pro Ser Leu Pro Pro Glu Pro Lys Thr
                305                 310                 315
Thr Lys Leu Gly Gln Arg Arg Glu Ser Ser Arg Pro Val Lys Pro
                320                 325                 330
Pro Lys Lys Asp Val Pro Asp Ser Gln Gln His Pro Ala Pro Glu
                335                 340                 345
Lys Ser Ser Lys Val Ser Glu Gln Leu Lys Cys Cys Ser Gly Ile
                350                 355                 360
Leu Lys Glu Met Phe Ala Lys Lys His Ala Ala Tyr Ala Trp Pro
                365                 370                 375
Phe Tyr Lys Pro Val Asp Val Glu Ala Leu Gly Leu His Asp Tyr
                380                 385                 390
Cys Asp Ile Ile Lys His Pro Met Asp Met Ser Thr Ile Lys Ser
                395                 400                 405
Lys Leu Glu Ala Arg Glu Tyr Arg Asp Ala Gln Glu Phe Gly Ala
                410                 415                 420
Asp Val Arg Leu Met Phe Ser Asn Cys Tyr Lys Tyr Asn Pro Pro
                425                 430                 435
Asp His Glu Val Val Ala Met Ala Arg Lys Leu Gln Asp Val Phe
                440                 445                 450
Glu Met Arg Phe Ala Lys Met Pro Asp Glu Pro Glu Glu Pro Val
                455                 460                 465
Val Ala Val Ser Ser Pro Ala Val Pro Pro Pro Thr Lys Val Val
                470                 475                 480
Ala Pro Pro Ser Ser Ser Asp Ser Ser Ser Asp Ser Ser Ser Asp
                485                 490                 495
Ser Asp Ser Ser Thr Asp Asp Ser Glu Glu Glu Arg Ala Gln Arg
                500                 505                 510
Leu Ala Glu Leu Gln Glu Gln Leu Lys Ala Val His Glu Gln Leu
                515                 520                 525
Ala Ala Leu Ser Gln Pro Gln Gln Asn Lys Pro Lys Lys Lys Glu
                530                 535                 540
Lys Asp Lys Lys Glu Lys Lys Lys Glu Lys His Lys Arg Lys Glu
                545                 550                 555
Glu Val Glu Glu Asn Lys Lys Ser Lys Ala Lys Glu Pro Pro Pro
                560                 565                 570
Lys Lys Thr Lys Lys Asn Asn Ser Ser Asn Ser Asn Val Ser Lys
                575                 580                 585
Lys Glu Pro Ala Pro Met Lys Ser Lys Pro Pro Pro Thr Tyr Glu
                590                 595                 600
Ser Glu Glu Glu Asp Lys Cys Lys Pro Met Ser Tyr Glu Glu Lys
                605                 610                 615
Arg Gln Leu Ser Leu Asp Ile Asn Lys Leu Pro Gly Glu Lys Leu
                620                 625                 630
```

```
Gly Arg Val Val His Ile Ile Gln Ser Arg Glu Pro Ser Leu Lys
                635                 640                 645
Asn Ser Asn Pro Asp Glu Ile Glu Ile Asp Phe Glu Thr Leu Lys
                650                 655                 660
Pro Ser Thr Leu Arg Glu Leu Gly Ala Leu Cys His Leu Leu Phe
                665                 670                 675
Ala Glu Glu Lys Glu Thr Phe Lys Leu Arg Lys Leu Met
                680                 685
```

```
<210> 23
<211> 439
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2100530
```

```
<400> 23
Met Gly Ser Gln Glu Val Leu Gly His Ala Ala Arg Leu Ala Ser
  1               5                  10                  15
Ser Gly Leu Leu Leu Gln Val Leu Phe Arg Leu Ile Thr Phe Val
                 20                  25                  30
Leu Asn Ala Phe Ile Leu Arg Phe Leu Ser Lys Glu Ile Val Gly
                 35                  40                  45
Val Val Asn Val Arg Leu Thr Leu Leu Tyr Ser Thr Thr Leu Phe
                 50                  55                  60
Leu Ala Arg Glu Ala Phe Arg Arg Ala Cys Leu Ser Gly Gly Thr
                 65                  70                  75
Gln Arg Asp Trp Ser Gln Thr Leu Asn Leu Leu Trp Leu Thr Val
                 80                  85                  90
Pro Leu Gly Val Phe Trp Ser Leu Phe Leu Gly Trp Ile Trp Leu
                 95                 100                 105
Gln Leu Leu Glu Val Pro Asp Pro Asn Val Val Pro His Tyr Ala
                110                 115                 120
Thr Gly Val Val Leu Phe Gly Leu Ser Ala Val Val Glu Leu Leu
                125                 130                 135
Gly Glu Pro Phe Trp Val Leu Ala Gln Ala His Met Phe Val Lys
                140                 145                 150
Leu Lys Val Ile Ala Glu Ser Leu Ser Val Ile Leu Lys Ser Val
                155                 160                 165
Leu Thr Ala Phe Leu Val Leu Trp Leu Pro His Trp Gly Leu Tyr
                170                 175                 180
Ile Phe Ser Leu Ala Gln Leu Phe Tyr Thr Thr Val Leu Val Leu
                185                 190                 195
Cys Tyr Val Ile Tyr Phe Thr Lys Leu Leu Gly Ser Pro Glu Ser
                200                 205                 210
Thr Lys Leu Gln Thr Leu Pro Val Ser Arg Ile Thr Asp Leu Leu
                215                 220                 225
Pro Asn Ile Thr Arg Asn Gly Ala Phe Ile Asn Trp Lys Glu Ala
```

```
                    230                     235                     240
Lys Leu Thr Trp Ser Phe Phe Lys Gln Ser Phe Leu Lys Gln Ile
                    245                     250                     255
Leu Thr Glu Gly Glu Arg Tyr Val Met Thr Phe Leu Asn Val Leu
                    260                     265                     270
Asn Phe Gly Asp Gln Gly Val Tyr Asp Ile Val Asn Asn Leu Gly
                    275                     280                     285
Ser Leu Val Ala Arg Leu Ile Phe Gln Pro Ile Glu Glu Ser Phe
                    290                     295                     300
Tyr Ile Phe Phe Ala Lys Val Leu Glu Arg Gly Lys Asp Ala Thr
                    305                     310                     315
Leu Gln Lys Gln Glu Asp Val Ala Val Ala Ala Ala Val Leu Glu
                    320                     325                     330
Ser Leu Leu Lys Leu Ala Leu Leu Ala Gly Leu Thr Ile Thr Val
                    335                     340                     345
Phe Gly Phe Ala Tyr Ser Gln Leu Ala Leu Asp Ile Tyr Gly Gly
                    350                     355                     360
Thr Met Leu Ser Ser Gly Ser Gly Pro Val Leu Leu Arg Ser Tyr
                    365                     370                     375
Cys Leu Tyr Val Leu Leu Leu Ala Ile Asn Gly Val Thr Glu Cys
                    380                     385                     390
Phe Thr Phe Ala Ala Met Ser Lys Glu Glu Val Asp Arg Tyr Ser
                    395                     400                     405
Ser Ala Val Ser Arg Ala Gly Gln Pro Asp Trp His Thr Leu Leu
                    410                     415                     420
Trp Gly Pro Ser Val Trp Glu Gln Leu Ser Gly Gln His Xaa Ser
                    425                     430                     435
Gln Arg Pro Ser
```

```
<210> 24
<211> 192
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2357636


<400> 24
Met Thr Ala Val Gly Val Gln Ala Gln Arg Pro Leu Gly Gln Arg
  1               5                  10                  15
Gln Pro Arg Arg Ser Phe Phe Glu Ser Phe Ile Arg Thr Leu Ile
                 20                  25                  30
Ile Thr Cys Val Ala Leu Ala Val Val Leu Ser Ser Val Ser Ile
                 35                  40                  45
Cys Asp Gly His Trp Leu Leu Ala Glu Asp Arg Leu Phe Gly Leu
                 50                  55                  60
Trp His Phe Cys Thr Thr Thr Asn Gln Ser Val Pro Ile Cys Phe
                 65                  70                  75
Arg Asp Leu Gly Gln Ala His Val Pro Gly Leu Ala Val Gly Met
                 80                  85                  90
Gly Leu Val Arg Ser Val Gly Ala Leu Ala Val Val Ala Ala Ile
                 95                 100                 105
Phe Gly Leu Glu Phe Leu Met Val Ser Gln Leu Cys Glu Asp Lys
```

```
                110                 115                 120
His Ser Gln Cys Lys Trp Val Met Gly Ser Ile Leu Leu Leu Val
                125                 130                 135
Ser Phe Val Leu Ser Ser Gly Gly Leu Leu Gly Phe Val Ile Leu
                140                 145                 150
Leu Arg Asn Gln Val Thr Leu Ile Gly Phe Thr Leu Met Phe Trp
                155                 160                 165
Cys Glu Phe Thr Ala Ser Phe Leu Leu Phe Leu Asn Ala Ile Ser
                170                 175                 180
Gly Leu His Ile Asn Ser Ile Thr His Pro Trp Glu
                185                 190
```

<210> 25
<211> 175
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2365230

<400> 25

```
Met Lys Glu Val Thr Arg Thr Trp Lys Ile Val Gly Gly Val Thr
 1               5                  10                  15
His Ala Asn Ser Tyr Tyr Lys Asn Gly Trp Ile Val Met Ile Ala
                20                  25                  30
Ile Gly Trp Ala Arg Gly Ala Gly Gly Thr Ile Ile Thr Asn Phe
                35                  40                  45
Glu Arg Leu Val Lys Gly Asp Trp Lys Pro Glu Gly Asp Glu Trp
                50                  55                  60
Leu Lys Met Ser Tyr Pro Ala Lys Val Thr Leu Leu Gly Ser Val
                65                  70                  75
Ile Phe Thr Phe Gln His Thr Gln His Leu Ala Ile Ser Lys His
                80                  85                  90
Asn Leu Met Phe Leu Tyr Thr Ile Phe Ile Val Ala Thr Lys Ile
                95                 100                 105
Thr Met Met Thr Thr Gln Thr Ser Thr Met Thr Phe Ala Pro Phe
                110                 115                 120
Glu Asp Thr Leu Ser Trp Met Leu Phe Gly Trp Gln Gln Pro Phe
                125                 130                 135
Ser Ser Cys Glu Lys Lys Ser Glu Ala Lys Ser Pro Ser Asn Gly
                140                 145                 150
Val Gly Ser Leu Ala Ser Lys Pro Val Asp Val Ala Ser Asp Asn
                155                 160                 165
Val Lys Lys Lys His Thr Lys Lys Asn Glu
                170                 175
```

<210> 26
<211> 91
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2455121

<400> 26
Met Tyr Pro Pro Pro Pro Pro Pro Pro His Arg Asp Phe Ile Ser
1 5 10 15
Val Thr Leu Ser Phe Gly Glu Ser Tyr Asp Asn Ser Lys Ser Trp
20 25 30
Arg Arg Arg Ser Cys Trp Arg Lys Trp Lys Gln Leu Ser Arg Leu
35 40 45
Gln Arg Asn Met Ile Leu Phe Leu Leu Ala Phe Leu Leu Phe Cys
50 55 60
Gly Leu Leu Phe Tyr Ile Asn Leu Ala Asp His Trp Lys Ala Leu
65 70 75
Ala Phe Arg Leu Gly Glu Glu Gln Lys Met Arg Pro Glu Ile Ala
80 85 90
Gly

<210> 27
<211> 214
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2472514

<400> 27
Met Gln Pro Thr Ser Trp Ala Val Ser Cys Gly Leu Arg Pro Leu
1 5 10 15
Pro Ser Trp Lys Pro Gln Gly Gly Glu Gly Arg Gly Gly Glu Glu
20 25 30
Arg Arg Gly Thr Val Met Gly Pro Trp Ser Arg Val Arg Val Ala
35 40 45
Lys Cys Gln Met Leu Val Thr Cys Phe Phe Ile Leu Leu Leu Gly
50 55 60
Leu Ser Val Ala Thr Met Val Thr Leu Thr Tyr Phe Gly Ala His
65 70 75
Phe Ala Val Ile Arg Arg Ala Ser Leu Glu Lys Asn Pro Tyr Gln
80 85 90
Ala Val His Gln Trp Ala Phe Ser Ala Gly Leu Ser Leu Val Gly
95 100 105
Leu Leu Thr Leu Gly Ala Val Leu Ser Ala Ala Ala Thr Val Arg
110 115 120
Glu Ala Gln Gly Leu Met Ala Gly Gly Phe Leu Cys Phe Ser Leu
125 130 135
Ala Phe Cys Ala Gln Val Gln Val Val Phe Trp Arg Leu His Ser
140 145 150
Pro Thr Gln Val Glu Asp Ala Met Leu Asp Thr Tyr Asp Leu Val
155 160 165
Tyr Glu Gln Ala Met Lys Gly Thr Ser His Val Arg Arg Gln Glu
170 175 180
Leu Ala Ala Ile Gln Asp Val Val Ser Val Gly Thr Ala Gly Trp
185 190 195
Gln Gly Gly Gln Leu Leu Leu Gly Leu Gln Phe Arg Glu Gln Ala

```
                200                 205                 210
Gln Gly Gly Gln
```

<210> 28
<211> 250
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2543486

<400> 28

```
Met Ser Val Ile Phe Phe Ala Cys Val Val Arg Val Arg Asp Gly
  1               5                  10                  15
Leu Pro Leu Ser Ala Ser Thr Asp Phe Tyr His Thr Gln Asp Phe
                 20                  25                  30
Leu Glu Trp Arg Arg Arg Leu Lys Ser Leu Ala Leu Arg Leu Ala
                 35                  40                  45
Gln Tyr Pro Gly Arg Gly Ser Ala Glu Gly Cys Asp Phe Ser Ile
                 50                  55                  60
His Phe Ser Ser Phe Gly Asp Val Ala Cys Met Ala Ile Cys Ser
                 65                  70                  75
Cys Gln Cys Pro Ala Ala Met Ala Phe Cys Phe Leu Glu Thr Leu
                 80                  85                  90
Trp Trp Glu Phe Thr Ala Ser Tyr Asp Thr Thr Cys Ile Gly Leu
                 95                 100                 105
Ala Ser Arg Pro Tyr Ala Phe Leu Glu Phe Asp Ser Ile Ile Gln
                110                 115                 120
Lys Val Lys Trp His Phe Asn Tyr Val Ser Ser Ser Gln Met Glu
                125                 130                 135
Cys Ser Leu Glu Lys Ile Gln Glu Glu Leu Lys Leu Gln Pro Pro
                140                 145                 150
Ala Val Leu Thr Leu Glu Asp Thr Asp Val Ala Asn Gly Val Met
                155                 160                 165
Asn Gly His Thr Pro Met His Leu Glu Pro Ala Pro Asn Phe Arg
                170                 175                 180
Met Glu Pro Val Thr Ala Leu Gly Ile Leu Ser Leu Ile Leu Asn
                185                 190                 195
Ile Met Cys Ala Ala Leu Asn Leu Ile Arg Gly Val His Leu Ala
                200                 205                 210
Glu His Ser Leu Gln Val Ala His Glu Glu Ile Gly Asn Ile Leu
                215                 220                 225
Ala Phe Leu Val Pro Phe Val Ala Cys Ile Phe Gln Asp Pro Arg
                230                 235                 240
Ser Trp Phe Cys Trp Leu Asp Gln Thr Ser
                245                 250
```

<210> 29
<211> 84
<212> PRT
<213> Homo sapiens

<220>

<221> misc_feature
<223> Incyte Clone No: 2778171

<400> 29
Met Ala Thr Gly Thr Asp Gln Val Val Gly Leu Gly Leu Val Ala
1   5   10   15
Val Ser Leu Ile Ile Phe Thr Tyr Tyr Thr Ala Trp Val Ile Leu
                20   25   30
Leu Pro Phe Ile Asp Ser Gln His Val Ile His Lys Tyr Phe Leu
                35   40   45
Pro Arg Ala Tyr Ala Val Ala Ile Pro Leu Ala Ala Gly Leu Leu
                50   55   60
Leu Leu Leu Phe Val Gly Leu Phe Ile Ser Tyr Val Met Leu Lys
                65   70   75
Ser Lys Arg Val Thr Lys Lys Ala Gln
                80

<210> 30
<211> 277
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2799575

<400> 30
Met Ala Ser Ala Glu Leu Asp Tyr Thr Ile Glu Ile Pro Asp Gln
1   5   10   15
Pro Cys Trp Ser Gln Lys Asn Ser Pro Ser Pro Gly Gly Lys Glu
                20   25   30
Ala Glu Thr Arg Gln Pro Val Val Ile Leu Leu Gly Trp Gly Gly
                35   40   45
Cys Lys Asp Lys Asn Leu Ala Lys Tyr Ser Ala Ile Tyr His Lys
                50   55   60
Arg Gly Cys Ile Val Ile Arg Tyr Thr Ala Pro Trp His Met Val
                65   70   75
Phe Phe Ser Glu Ser Leu Gly Ile Pro Ser Leu Arg Val Leu Ala
                80   85   90
Gln Lys Leu Leu Glu Leu Leu Phe Asp Tyr Glu Ile Glu Lys Glu
                95   100   105
Pro Leu Leu Phe His Val Phe Ser Asn Gly Gly Val Met Leu Tyr
                110   115   120
Arg Tyr Val Leu Glu Leu Leu Gln Thr Arg Arg Phe Cys Arg Leu
                125   130   135
Arg Val Val Gly Thr Ile Phe Asp Ser Ala Pro Gly Asp Ser Asn
                140   145   150
Leu Val Gly Ala Leu Arg Ala Leu Ala Ala Ile Leu Glu Arg Arg
                155   160   165
Ala Ala Met Leu Arg Leu Leu Leu Leu Val Ala Phe Ala Leu Val
                170   175   180
Val Val Leu Phe His Val Leu Leu Ala Pro Ile Thr Ala Leu Phe
                185   190   195
His Thr His Phe Tyr Asp Arg Leu Gln Asp Ala Gly Ser Arg Trp

```
                200                 205                 210
Pro Glu Leu Tyr Leu Tyr Ser Arg Ala Asp Glu Val Val Leu Ala
                215                 220                 225
Arg Asp Ile Glu Arg Met Val Glu Ala Arg Leu Ala Arg Arg Val
                230                 235                 240
Leu Ala Arg Ser Val Asp Phe Val Ser Ser Ala His Val Ser His
                245                 250                 255
Leu Arg Asp Tyr Pro Thr Tyr Tyr Thr Ser Leu Cys Val Asp Phe
                260                 265                 270
Met Arg Asn Cys Val Arg Cys
                275
```

<210> 31
<211> 273
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2804955

<400> 31

```
Met Ser Gly Ser Gln Ser Glu Val Ala Pro Ser Pro Gln Ser Pro
  1             5                   10                  15
Arg Ser Pro Glu Met Gly Arg Asp Leu Arg Pro Gly Ser Arg Val
                20                  25                  30
Leu Leu Leu Leu Leu Leu Leu Leu Leu Val Tyr Leu Thr Gln Pro
                35                  40                  45
Gly Asn Gly Asn Glu Gly Ser Val Thr Gly Ser Cys Tyr Cys Gly
                50                  55                  60
Lys Arg Ile Ser Ser Asp Ser Pro Pro Ser Val Gln Phe Met Asn
                65                  70                  75
Arg Leu Arg Lys His Leu Arg Ala Tyr His Arg Cys Leu Tyr Tyr
                80                  85                  90
Thr Arg Phe Gln Leu Leu Ser Trp Ser Val Cys Gly Gly Asn Lys
                95                  100                 105
Asp Pro Trp Val Gln Glu Leu Met Ser Cys Leu Asp Leu Lys Glu
                110                 115                 120
Cys Gly His Ala Tyr Ser Gly Ile Val Ala His Gln Lys His Leu
                125                 130                 135
Leu Pro Thr Ser Pro Pro Ile Ser Gln Ala Ser Glu Gly Ala Ser
                140                 145                 150
Ser Asp Ile His Thr Pro Ala Gln Met Leu Leu Ser Thr Leu Gln
                155                 160                 165
Ser Thr Gln Arg Pro Thr Leu Pro Val Gly Ser Leu Ser Ser Asp
                170                 175                 180
Lys Glu Leu Thr Arg Pro Asn Glu Thr Thr Ile His Thr Ala Gly
                185                 190                 195
His Ser Leu Ala Ala Gly Pro Glu Ala Gly Glu Asn Gln Lys Gln
                200                 205                 210
Pro Glu Lys Asn Ala Gly Pro Thr Ala Arg Thr Ser Ala Thr Val
                215                 220                 225
Pro Val Leu Cys Leu Leu Ala Ile Ile Phe Ile Leu Thr Ala Ala
```

```
                    230                 235                 240
Leu Ser Tyr Val Leu Cys Lys Arg Arg Arg Gly Gln Ser Pro Gln
                    245                 250                 255
Ser Ser Pro Asp Leu Pro Val His Tyr Ile Pro Val Ala Pro Asp
                    260                 265                 270
Ser Asn Thr


<210> 32
<211> 524
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2806395


<400> 32
Met Ser Gln Gly Ser Pro Gly Asp Trp Ala Pro Leu Asp Pro Thr
  1               5                  10                  15
Pro Gly Pro Pro Ala Ser Pro Asn Pro Phe Val His Glu Leu His
                 20                  25                  30
Leu Ser Arg Leu Gln Arg Val Lys Phe Cys Leu Leu Gly Ala Leu
                 35                  40                  45
Leu Ala Pro Ile Arg Val Leu Leu Ala Phe Ile Val Leu Phe Leu
                 50                  55                  60
Leu Trp Pro Phe Ala Trp Leu Gln Val Ala Gly Leu Ser Glu Glu
                 65                  70                  75
Gln Leu Gln Glu Pro Ile Thr Gly Trp Arg Lys Thr Val Cys His
                 80                  85                  90
Asn Gly Val Leu Gly Leu Ser Arg Leu Leu Phe Phe Leu Leu Gly
                 95                 100                 105
Phe Leu Arg Ile Arg Val Arg Gly Gln Arg Ala Ser Arg Leu Gln
                110                 115                 120
Ala Pro Val Leu Val Ala Ala Pro His Ser Thr Phe Phe Asp Pro
                125                 130                 135
Ile Val Leu Leu Pro Cys Asp Leu Pro Lys Val Val Ser Arg Ala
                140                 145                 150
Glu Asn Leu Ser Val Pro Val Ile Gly Ala Leu Leu Arg Phe Asn
                155                 160                 165
Gln Ala Ile Leu Val Ser Arg His Asp Pro Ala Ser Arg Arg Arg
                170                 175                 180
Val Val Glu Glu Val Arg Arg Arg Ala Thr Ser Gly Gly Lys Trp
                185                 190                 195
Pro Gln Val Leu Phe Phe Pro Glu Gly Thr Cys Ser Asn Lys Lys
                200                 205                 210
Ala Leu Leu Lys Phe Lys Pro Gly Ala Phe Ile Ala Gly Val Pro
                215                 220                 225
Val Gln Pro Val Leu Ile Arg Tyr Pro Asn Ser Leu Asp Thr Thr
                230                 235                 240
Ser Trp Ala Trp Arg Gly Pro Gly Val Leu Lys Val Leu Trp Leu
                245                 250                 255
Thr Ala Ser Gln Pro Cys Ser Ile Val Asp Val Glu Phe Leu Pro
                260                 265                 270
Val Tyr His Pro Ser Pro Glu Glu Ser Arg Asp Pro Thr Leu Tyr
                275                 280                 285
```

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Ala Asn Asn Val Gln Arg Val Met Ala Gln Ala Leu Gly Ile Pro
                290                 295                 300
Ala Thr Glu Cys Glu Phe Val Gly Ser Leu Pro Val Ile Val Val
                305                 310                 315
Gly Arg Leu Lys Val Ala Leu Glu Pro Gln Leu Trp Glu Leu Gly
                320                 325                 330
Lys Val Leu Arg Lys Ala Gly Leu Ser Ala Gly Tyr Val Asp Ala
                335                 340                 345
Gly Ala Glu Pro Gly Arg Ser Arg Met Ile Ser Gln Glu Glu Phe
                350                 355                 360
Ala Arg Gln Leu Gln Leu Ser Asp Pro Gln Thr Val Ala Gly Ala
                365                 370                 375
Phe Gly Tyr Phe Gln Gln Asp Thr Lys Gly Leu Val Asp Phe Arg
                380                 385                 390
Asp Val Ala Leu Ala Leu Ala Ala Leu Asp Gly Gly Arg Ser Leu
                395                 400                 405
Glu Glu Leu Thr Arg Leu Ala Phe Glu Leu Phe Ala Glu Glu Gln
                410                 415                 420
Ala Glu Gly Pro Asn Arg Leu Leu Tyr Lys Asp Gly Phe Ser Thr
                425                 430                 435
Ile Leu His Leu Leu Leu Gly Ser Pro His Pro Ala Ala Thr Ala
                440                 445                 450
Leu His Ala Glu Leu Cys Gln Ala Gly Ser Ser Gln Gly Leu Ser
                455                 460                 465
Leu Cys Gln Phe Gln Asn Phe Ser Leu His Asp Pro Leu Tyr Gly
                470                 475                 480
Lys Leu Phe Ser Thr Tyr Leu Arg Pro Pro His Thr Ser Arg Gly
                485                 490                 495
Thr Ser Gln Thr Pro Asn Ala Ser Ser Pro Gly Asn Pro Thr Ala
                500                 505                 510
Leu Ala Asn Gly Thr Val Gln Ala Pro Lys Gln Lys Gly Asp
                515                 520


<210> 33
<211> 257
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2836858


<400> 33
Met Asp Phe Ser Arg Leu His Met Tyr Ser Pro Pro Gln Cys Val
  1               5                  10                  15
Pro Glu Asn Thr Gly Tyr Thr Tyr Ala Leu Ser Ser Ser Tyr Ser
                 20                  25                  30
Ser Asp Ala Leu Asp Phe Glu Thr Glu His Lys Leu Asp Pro Val
                 35                  40                  45
Phe Asp Ser Pro Arg Met Ser Arg Arg Ser Leu Arg Leu Ala Thr
                 50                  55                  60
Thr Ala Cys Thr Leu Gly Asp Gly Glu Ala Val Gly Ala Asp Ser
                 65                  70                  75
Gly Thr Ser Ser Ala Val Ser Leu Lys Asn Arg Ala Ala Arg Thr
                 80                  85                  90
```

Thr Lys Gln Arg Arg Ser Thr Asn Lys Ser Ala Phe Ser Ile Asn
95 100 105
His Val Ser Arg Gln Val Thr Ser Ser Gly Val Ser His Gly Gly
110 115 120
Thr Val Ser Leu Gln Asp Ala Val Thr Arg Arg Pro Pro Val Leu
125 130 135
Asp Glu Ser Trp Ile Arg Glu Gln Thr Thr Val Asp His Phe Trp
140 145 150
Gly Leu Asp Asp Asp Gly Asp Leu Lys Gly Gly Asn Lys Ala Ala
155 160 165
Ile Gln Gly Asn Gly Asp Val Gly Ala Ala Ala Ala Thr Ala His
170 175 180
Asn Gly Phe Ser Cys Ser Asn Cys Ser Met Leu Ser Glu Arg Lys
185 190 195
Asp Val Leu Thr Ala His Pro Ala Ala Pro Gly Pro Val Ser Arg
200 205 210
Val Tyr Ser Arg Asp Arg Asn Gln Lys Cys Lys Ser Gln Ser Phe
215 220 225
Lys Thr Gln Lys Lys Val Cys Phe Pro Asn Leu Ile Phe Pro Phe
230 235 240
Cys Lys Ser Gln Cys Leu His Tyr Leu Ser Trp Arg Leu Lys Ile
245 250 255
Ile Pro

<210> 34
<211> 274
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2844513

<400> 34
Met Arg Ala Ala Gly Val Gly Leu Val Asp Cys His Cys His Leu
1 5 10 15
Ser Ala Pro Asp Phe Asp Arg Asp Leu Asp Asp Val Leu Glu Lys
20 25 30
Ala Lys Lys Ala Asn Val Val Ala Leu Val Ala Val Ala Glu His
35 40 45
Ser Gly Glu Phe Glu Lys Ile Met Gln Leu Ser Glu Arg Tyr Asn
50 55 60
Gly Phe Val Leu Pro Cys Leu Gly Val His Pro Val Gln Gly Leu
65 70 75
Pro Pro Glu Asp Gln Arg Ser Val Thr Leu Lys Asp Leu Asp Val
80 85 90
Ala Leu Pro Ile Ile Glu Asn Tyr Lys Asp Arg Leu Leu Ala Ile
95 100 105
Gly Glu Val Gly Leu Asp Phe Ser Pro Arg Phe Ala Gly Thr Gly
110 115 120
Glu Gln Lys Glu Glu Gln Arg Gln Val Leu Ile Arg Gln Ile Gln
125 130 135
Leu Ala Lys Arg Leu Asn Leu Pro Val Asn Val His Ser Arg Ser
140 145 150
Ala Gly Arg Pro Thr Ile Asn Leu Leu Gln Glu Gln Gly Ala Glu

```
                    155                 160                 165
Lys Val Leu Leu His Ala Phe Asp Gly Arg Pro Ser Val Ala Met
                    170                 175                 180
Glu Gly Val Arg Ala Gly Tyr Phe Phe Ser Ile Pro Pro Ser Ile
                    185                 190                 195
Ile Arg Ser Gly Gln Lys Gln Lys Leu Val Lys Gln Leu Pro Leu
                    200                 205                 210
Thr Ser Ile Cys Leu Glu Thr Asp Ser Pro Ala Leu Gly Pro Glu
                    215                 220                 225
Lys Gln Val Arg Asn Glu Pro Trp Asn Ile Ser Ile Ser Ala Glu
                    230                 235                 240
Tyr Ile Ala Gln Val Lys Gly Ile Ser Val Glu Glu Val Ile Glu
                    245                 250                 255
Val Thr Thr Gln Asn Ala Leu Lys Leu Phe Pro Lys Leu Arg His
                    260                 265                 270
Leu Leu Gln Lys


<210> 35
<211> 281
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 3000380


<400> 35
Met Ser Glu Pro Gln Pro Asp Leu Glu Pro Pro Gln His Gly Leu
  1               5                  10                  15
Tyr Met Leu Phe Leu Leu Val Leu Val Phe Phe Leu Met Gly Leu
                 20                  25                  30
Val Gly Phe Met Ile Cys His Val Leu Lys Lys Lys Gly Tyr Arg
                 35                  40                  45
Cys Arg Thr Ser Arg Gly Ser Glu Pro Asp Asp Ala Gln Leu Gln
                 50                  55                  60
Pro Pro Glu Asp Asp Asp Met Asn Glu Asp Thr Val Glu Arg Ile
                 65                  70                  75
Val Arg Cys Ile Ile Gln Asn Glu Val Trp Met Pro Pro Pro Ala
                 80                  85                  90
Cys Arg Thr Glu Pro Pro Pro Ile Ile Thr Gln Cys Thr Trp Ala
                 95                 100                 105
Leu Gln Pro Leu Ala Val His Cys Ser Arg Ser Lys Arg Pro Pro
                110                 115                 120
Leu Val Arg Gln Gly Arg Ser Lys Glu Gly Lys Ser Arg Pro Arg
                125                 130                 135
Thr Gly Glu Thr Thr Val Phe Ser Val Gly Arg Phe Arg Val Thr
                140                 145                 150
His Ile Glu Lys Arg Tyr Gly Leu His Glu His Arg Asp Gly Ser
                155                 160                 165
Pro Thr Asp Arg Ser Trp Gly Ser Arg Gly Gly Gln Asp Pro Gly
                170                 175                 180
Gly Gly Gln Gly Ser Gly Gly Gly His Pro Lys Ala Gly Met Leu
                185                 190                 195
```

Pro Trp Arg Gly Cys Pro Pro Glu Arg Pro Gln Pro Gln Val Leu
200 205 210
Ala Ser Pro Pro Val Gln Asn Gly Gly Leu Arg Asp Ser Ser Leu
215 220 225
Thr Pro Arg Ala Leu Glu Gly Asn Pro Arg Ala Ser Ala Glu Pro
230 235 240
Thr Leu Arg Ala Gly Gly Arg Gly Pro Ser Pro Gly Leu Pro Thr
245 250 255
Gln Glu Ala Asn Gly Gln Pro Ser Lys Pro Asp Thr Ser Asp His
260 265 270
Gln Val Ser Leu Pro Gln Gly Ala Gly Ser Met
275 280

<210> 36
<211> 335
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 182532

<400> 36
Met Gly Pro Leu Ser Ala Pro Pro Cys Thr His Leu Ile Thr Trp
1 5 10 15
Lys Gly Val Leu Leu Thr Ala Ser Leu Leu Asn Phe Trp Asn Pro
20 25 30
Pro Thr Thr Ala Gln Val Thr Ile Glu Ala Gln Pro Pro Lys Val
35 40 45
Ser Glu Gly Lys Asp Val Leu Leu Leu Val His Asn Leu Pro Gln
50 55 60
Asn Leu Ala Gly Tyr Ile Trp Tyr Lys Gly Gln Met Thr Tyr Val
65 70 75
Tyr His Tyr Ile Ile Ser Tyr Ile Val Asp Gly Lys Ile Ile Ile
80 85 90
Tyr Gly Pro Ala Tyr Ser Gly Arg Glu Arg Val Tyr Ser Asn Ala
95 100 105
Ser Leu Leu Ile Gln Asn Val Thr Gln Glu Asp Ala Gly Ser Tyr
110 115 120
Thr Leu His Ile Ile Lys Arg Gly Asp Gly Thr Arg Gly Glu Thr
125 130 135
Gly His Phe Thr Phe Thr Leu Tyr Leu Glu Thr Pro Lys Pro Ser
140 145 150
Ile Ser Ser Ser Asn Leu Tyr Pro Arg Glu Asp Met Glu Ala Val
155 160 165
Ser Leu Thr Cys Asp Pro Glu Thr Pro Asp Ala Ser Tyr Leu Trp
170 175 180
Trp Met Asn Gly Gln Ser Leu Pro Met Thr His Ser Leu Gln Leu
185 190 195
Ser Lys Asn Lys Arg Thr Leu Phe Leu Phe Gly Val Thr Lys Tyr
200 205 210
Thr Ala Gly Pro Tyr Glu Cys Glu Ile Arg Asn Pro Val Ser Gly
215 220 225
Ile Arg Ser Asp Pro Val Thr Leu Asn Val Leu Tyr Gly Pro Asp
230 235 240

Leu Pro Ser Ile Tyr Pro Ser Phe Thr Tyr Tyr Arg Ser Gly Glu
245 250 255
Asn Leu Tyr Leu Ser Cys Phe Ala Glu Ser Asn Pro Arg Ala Gln
260 265 270
Tyr Ser Trp Thr Ile Asn Gly Lys Phe Gln Leu Ser Gly Gln Lys
275 280 285
Leu Phe Ile Pro Gln Ile Thr Thr Lys His Ser Gly Leu Tyr Ala
290 295 300
Cys Ser Val Arg Asn Ser Ala Thr Gly Met Glu Ser Ser Lys Ser
305 310 315
Met Thr Val Lys Val Ser Ala Pro Ser Gly Thr Gly His Leu Pro
320 325 330
Gly Leu Asn Pro Leu
335

<210> 37
<211> 280
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 239589

<400> 37
Met Asp Leu Gln Gly Arg Gly Val Pro Ser Ile Asp Arg Leu Arg
1 5 10 15
Val Leu Leu Met Leu Phe His Thr Met Ala Gln Ile Met Ala Glu
20 25 30
Gln Glu Val Glu Asn Leu Ser Gly Leu Ser Thr Asn Pro Glu Lys
35 40 45
Asp Ile Phe Val Val Arg Glu Asn Gly Thr Thr Cys Leu Met Ala
50 55 60
Glu Phe Ala Ala Lys Phe Ile Val Pro Tyr Asp Val Trp Ala Ser
65 70 75
Asn Tyr Val Asp Leu Ile Thr Glu Gln Ala Asp Ile Ala Leu Thr
80 85 90
Arg Gly Ala Glu Val Lys Gly Arg Cys Gly His Ser Gln Ser Glu
95 100 105
Leu Gln Val Phe Trp Val Asp Arg Ala Tyr Ala Leu Lys Met Leu
110 115 120
Phe Val Lys Glu Ser His Asn Met Ser Lys Gly Pro Glu Ala Thr
125 130 135
Trp Arg Leu Ser Lys Val Gln Phe Val Tyr Asp Ser Ser Glu Lys
140 145 150
Thr His Phe Lys Asp Ala Val Ser Ala Gly Lys His Thr Ala Asn
155 160 165
Ser His His Leu Ser Ala Leu Val Thr Pro Ala Gly Lys Ser Tyr
170 175 180
Glu Cys Gln Ala Gln Gln Thr Ile Ser Leu Ala Ser Ser Asp Pro
185 190 195
Gln Lys Thr Val Thr Met Ile Leu Ser Ala Val His Ile Gln Pro
200 205 210
Phe Asp Ile Ile Ser Asp Phe Val Phe Ser Glu Glu His Lys Cys
215 220 225

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Pro Val Asp Glu Arg Glu Gln Leu Glu Glu Thr Leu Pro Leu Ile
                230                 235                 240
Leu Gly Leu Ile Leu Gly Leu Val Ile Met Val Thr Leu Ala Ile
                245                 250                 255
Tyr His Val His His Lys Met Thr Ala Asn Gln Val Gln Ile Pro
                260                 265                 270
Arg Asp Arg Ser Gln Tyr Lys His Met Gly
                275                 280


<210> 38
<211> 210
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 1671302


<400> 38
Met Ser Arg Met Phe Cys Gln Ala Ala Arg Val Asp Leu Thr Leu
  1               5                  10                  15
Asp Pro Asp Thr Ala His Pro Ala Leu Met Leu Ser Pro Asp Arg
                 20                  25                  30
Arg Gly Val Arg Leu Ala Glu Arg Arg Gln Glu Val Ala Asp His
                 35                  40                  45
Pro Lys Arg Phe Ser Ala Asp Cys Cys Val Leu Gly Ala Gln Gly
                 50                  55                  60
Phe Arg Ser Gly Arg His Tyr Trp Glu Val Glu Val Gly Gly Arg
                 65                  70                  75
Arg Gly Trp Ala Val Gly Ala Ala Arg Glu Ser Thr His His Lys
                 80                  85                  90
Glu Lys Val Gly Pro Gly Gly Ser Ser Val Gly Ser Gly Asp Ala
                 95                 100                 105
Ser Ser Ser Arg His His His Arg Arg Arg Arg Leu His Leu Pro
                110                 115                 120
Gln Gln Pro Leu Leu Gln Arg Glu Val Trp Cys Val Gly Thr Asn
                125                 130                 135
Gly Lys Arg Tyr Gln Ala Gln Ser Ser Thr Glu Gln Thr Leu Leu
                140                 145                 150
Ser Pro Ser Glu Lys Pro Arg Arg Phe Gly Val Tyr Leu Asp Tyr
                155                 160                 165
Glu Ala Gly Arg Leu Gly Phe Tyr Asn Ala Glu Thr Leu Ala His
                170                 175                 180
Val His Thr Phe Ser Ala Ala Phe Leu Gly Glu Arg Val Phe Pro
                185                 190                 195
Phe Phe Arg Val Leu Ser Lys Gly Thr Arg Ile Lys Leu Cys Pro
                200                 205                 210


<210> 39
<211> 279
<212> PRT
<213> Homo sapiens

<220>
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<221> misc_feature
<223> Incyte Clone No: 2041858

<400> 39
Met Glu Ala Val Val Asn Leu Tyr Gln Glu Val Met Lys His Ala
1 5 10 15
Asp Pro Arg Ile Gln Gly Tyr Pro Leu Met Gly Ser Pro Leu Leu
20 25 30
Met Thr Ser Ile Leu Leu Thr Tyr Val Tyr Phe Val Leu Ser Leu
35 40 45
Gly Pro Arg Ile Met Ala Asn Arg Lys Pro Phe Gln Leu Arg Gly
50 55 60
Phe Met Ile Val Tyr Asn Phe Ser Leu Val Ala Leu Ser Leu Tyr
65 70 75
Ile Val Tyr Glu Phe Leu Met Ser Gly Trp Leu Ser Thr Tyr Thr
80 85 90
Trp Arg Cys Asp Pro Val Asp Tyr Ser Asn Ser Pro Glu Ala Leu
95 100 105
Arg Met Val Arg Val Ala Trp Leu Phe Leu Phe Ser Lys Phe Ile
110 115 120
Glu Leu Met Asp Thr Val Ile Phe Ile Leu Arg Lys Lys Asp Gly
125 130 135
Gln Val Thr Phe Leu His Val Phe His His Ser Val Leu Pro Trp
140 145 150
Ser Trp Trp Trp Gly Val Lys Ile Ala Pro Gly Gly Met Gly Ser
155 160 165
Phe His Ala Met Ile Asn Ser Ser Val His Val Ile Met Tyr Leu
170 175 180
Tyr Tyr Gly Leu Ser Ala Phe Gly Pro Val Ala Gln Pro Tyr Leu
185 190 195
Trp Trp Lys Lys His Met Thr Ala Ile Gln Leu Ile Gln Phe Val
200 205 210
Leu Val Ser Leu His Ile Ser Gln Tyr Tyr Phe Met Ser Ser Cys
215 220 225
Asn Tyr Gln Tyr Pro Val Ile Ile His Leu Ile Trp Met Tyr Gly
230 235 240
Thr Ile Phe Phe Met Leu Phe Ser Asn Phe Trp Tyr His Ser Tyr
245 250 255
Thr Lys Gly Lys Arg Leu Pro Arg Ala Leu Gln Gln Asn Gly Ala
260 265 270
Pro Gly Ile Ala Lys Val Lys Ala Asn
275

<210> 40
<211> 154
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2198863

<400> 40
Met Gly Lys Ser Ala Ser Lys Gln Phe His Asn Glu Val Leu Lys

1 5 10 15
Ala His Asn Glu Tyr Arg Gln Lys His Gly Val Pro Pro Leu Lys
20 25 30
Leu Cys Lys Asn Leu Asn Arg Glu Ala Gln Gln Tyr Ser Glu Ala
35 40 45
Leu Ala Ser Thr Arg Ile Leu Lys His Ser Pro Glu Ser Ser Arg
50 55 60
Gly Gln Cys Gly Glu Asn Leu Ala Trp Ala Ser Tyr Asp Gln Thr
65 70 75
Gly Lys Glu Val Ala Asp Arg Trp Tyr Ser Glu Ile Lys Asn Tyr
80 85 90
Asn Phe Gln Gln Pro Gly Phe Thr Ser Gly Thr Gly His Phe Thr
95 100 105
Ala Met Val Trp Lys Asn Thr Lys Lys Met Gly Val Gly Lys Ala
110 115 120
Ser Ala Ser Asp Gly Ser Ser Phe Val Val Ala Arg Tyr Phe Pro
125 130 135
Ala Gly Asn Val Val Asn Glu Gly Phe Phe Glu Glu Asn Val Leu
140 145 150
Pro Pro Lys Lys

<210> 41
<211> 582
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 3250703

<400> 41
Met Lys Pro Asn Ile Ile Phe Val Leu Ser Leu Leu Leu Ile Leu
1 5 10 15
Glu Lys Gln Ala Ala Val Met Gly Gln Lys Gly Gly Ser Lys Gly
20 25 30
Arg Leu Pro Ser Glu Phe Ser Gln Phe Pro His Gly Gln Lys Gly
35 40 45
Gln His Tyr Ser Gly Gln Lys Gly Lys Gln Gln Thr Glu Ser Lys
50 55 60
Gly Ser Phe Ser Ile Gln Tyr Thr Tyr His Val Asp Ala Asn Asp
65 70 75
His Asp Gln Ser Arg Lys Ser Gln Gln Tyr Asp Leu Asn Ala Leu
80 85 90
His Lys Thr Thr Lys Ser Gln Arg His Leu Gly Gly Ser Gln Gln
95 100 105
Leu Leu His Asn Lys Gln Glu Gly Arg Asp His Asp Lys Ser Lys
110 115 120
Gly His Phe His Arg Val Val Ile His His Lys Gly Gly Lys Ala
125 130 135
His Arg Gly Thr Gln Asn Pro Ser Gln Asp Gln Gly Asn Ser Pro
140 145 150
Ser Gly Lys Gly Ile Ser Ser Gln Tyr Ser Asn Thr Glu Glu Arg
155 160 165

Leu Trp Val His Gly Leu Ser Lys Glu Gln Thr Ser Val Ser Gly
170 175 180
Ala Gln Lys Gly Arg Lys Gln Gly Gly Ser Gln Ser Ser Tyr Val
185 190 195
Leu Gln Thr Glu Glu Leu Val Ala Asn Lys Gln Gln Arg Glu Thr
200 205 210
Lys Asn Ser His Gln Asn Lys Gly His Tyr Gln Asn Val Val Glu
215 220 225
Val Arg Glu Glu His Ser Ser Lys Val Gln Thr Ser Leu Cys Pro
230 235 240
Ala His Gln Asp Lys Leu Gln His Gly Ser Lys Asp Ile Phe Ser
245 250 255
Thr Gln Asp Glu Leu Leu Val Tyr Asn Lys Asn Gln His Gln Thr
260 265 270
Lys Asn Leu Asn Gln Asp Gln Gln His Gly Arg Lys Ala Asn Lys
275 280 285
Ile Ser Tyr Gln Ser Ser Ser Thr Glu Glu Arg Arg Leu His Tyr
290 295 300
Gly Glu Asn Gly Val Gln Lys Asp Val Ser Gln Ser Ser Ile Tyr
305 310 315
Ser Gln Thr Glu Glu Lys Ile His Gly Lys Ser Gln Asn Gln Val
320 325 330
Thr Ile His Ser Gln Asp Gln Glu His Gly His Lys Glu Asn Lys
335 340 345
Ile Ser Tyr Gln Ser Ser Ser Thr Glu Glu Arg His Leu Asn Cys
350 355 360
Gly Glu Lys Gly Ile Gln Lys Gly Val Ser Lys Gly Ser Ile Ser
365 370 375
Ile Gln Thr Glu Glu Gln Ile His Gly Lys Ser Gln Asn Gln Val
380 385 390
Arg Ile Pro Ser Gln Ala Gln Glu Tyr Gly His Lys Glu Asn Lys
395 400 405
Ile Ser Tyr Gln Ser Ser Ser Thr Glu Glu Arg Arg Leu Asn Ser
410 415 420
Gly Glu Lys Asp Val Gln Lys Gly Val Ser Lys Gly Ser Ile Ser
425 430 435
Ile Gln Thr Glu Glu Lys Ile His Gly Lys Ser Gln Asn Gln Val
440 445 450
Thr Ile Pro Ser Gln Asp Gln Glu His Gly His Lys Glu Asn Lys
455 460 465
Met Ser Tyr Gln Ser Ser Ser Thr Glu Glu Arg Arg Leu Asn Tyr
470 475 480
Gly Gly Lys Ser Thr Gln Lys Asp Val Ser Gln Ser Ser Ile Ser
485 490 495
Phe Gln Ile Glu Lys Leu Val Glu Gly Lys Ser Gln Ile Gln Thr
500 505 510
Pro Asn Pro Asn Gln Asp Gln Trp Ser Gly Gln Asn Ala Lys Gly
515 520 525
Lys Ser Gly Gln Ser Ala Asp Ser Lys Gln Asp Leu Leu Ser His
530 535 540
Glu Gln Lys Gly Arg Tyr Lys Gln Glu Ser Ser Glu Ser His Asn
545 550 555
Ile Val Ile Thr Glu His Glu Val Ala Gln Asp Asp His Leu Thr
560 565 570
Gln Gln Tyr Asn Glu Asp Arg Asn Pro Ile Ser Thr
575 580

<210> 42
<211> 71
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 350287

<400> 42
Met Phe Thr Ala Pro Leu Phe Phe Phe Phe Phe Phe Glu Ile Ile
1 5 10 15
Asn Ser Met Arg Asn Leu Gly Leu Asn Ile Cys Leu Leu Cys Leu
20 25 30
Leu Ile Glu His His Ser Arg Pro Ser Val Cys Leu Pro Phe Thr
35 40 45
Pro Lys Ile Phe Thr Lys Lys Ile Leu Arg Gln Gln Val Thr Ile
50 55 60
Tyr Arg Cys Leu Asn Asp Phe Leu Ile Phe Ile
65 70

<210> 43
<211> 102
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 1618171

<400> 43
Met Ala Val Leu Pro Ser Val Leu Leu Val Tyr Ser Leu Phe Phe
1 5 10 15
Cys Leu Arg Phe Cys Met Leu Leu Leu Leu Pro Ser Tyr Ser His
20 25 30
Ser Arg Ser Gly Arg Gly Pro Gly Arg Tyr Gly His Ile Thr Leu
35 40 45
Ile Asp Val Ile His Val Ser Val Tyr Trp Phe Phe Glu Ala Leu
50 55 60
Ser Thr Phe Gln Ile Phe Tyr Tyr Cys Ile Thr Arg Thr Ile Thr
65 70 75
Val Arg Lys Gly Ile Val Val Ser Arg His Val Asn Glu Ala Gly
80 85 90
Val Ser Phe Val Ser Tyr Leu Cys Ile Asn Phe Lys
95 100

<210> 44
<211> 226
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 1625863

<400> 44
Met Pro Thr Thr Lys Lys Thr Leu Met Phe Leu Ser Ser Phe Phe
1 5 10 15
Thr Ser Leu Gly Ser Phe Ile Val Ile Cys Ser Ile Leu Gly Thr
20 25 30
Gln Ala Trp Ile Thr Ser Thr Ile Ala Val Arg Asp Ser Ala Ser
35 40 45
Asn Gly Ser Ile Phe Ile Thr Tyr Gly Leu Phe Arg Gly Glu Ser
50 55 60
Ser Glu Glu Leu Ser His Gly Leu Ala Glu Pro Lys Lys Lys Phe
65 70 75
Ala Val Leu Glu Ile Leu Asn Asn Ser Ser Gln Lys Thr Leu His
80 85 90
Ser Val Thr Ile Leu Phe Leu Val Leu Ser Leu Ile Thr Ser Leu
95 100 105
Leu Ser Ser Gly Phe Thr Phe Tyr Asn Ser Ile Ser Asn Pro Tyr
110 115 120
Gln Thr Phe Leu Gly Pro Thr Gly Val Tyr Thr Trp Asn Gly Leu
125 130 135
Gly Ala Ser Phe Val Phe Val Thr Met Ile Leu Phe Val Ala Asn
140 145 150
Thr Gln Ser Asn Gln Leu Ser Glu Glu Leu Phe Gln Met Leu Tyr
155 160 165
Pro Ala Thr Thr Ser Lys Gly Thr Thr His Ser Tyr Gly Tyr Ser
170 175 180
Phe Trp Leu Ile Leu Leu Val Ile Leu Leu Asn Ile Val Thr Val
185 190 195
Thr Ile Ile Ile Phe Tyr Gln Lys Ala Arg Tyr Gln Arg Lys Gln
200 205 210
Glu Gln Arg Lys Pro Met Glu Tyr Ala Pro Arg Asp Gly Ile Leu
215 220 225
Phe

<210> 45
<211> 154
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 1638353

<400> 45
Met Ala Leu Leu Leu Ser Val Leu Arg Val Leu Leu Gly Gly Phe
1 5 10 15
Phe Ala Leu Val Gly Leu Ala Lys Leu Ser Glu Glu Ile Ser Ala
20 25 30
Pro Val Ser Glu Arg Met Asn Ala Leu Phe Val Gln Phe Ala Glu
35 40 45
Val Phe Pro Leu Lys Val Phe Gly Tyr Gln Pro Asp Pro Leu Asn
50 55 60
Tyr Gln Ile Ala Val Gly Phe Leu Glu Leu Leu Ala Gly Leu Leu
65 70 75

```
Leu Val Met Gly Pro Pro Met Leu Gln Glu Ile Ser Asn Leu Phe
                 80                  85                  90
Leu Ile Leu Leu Met Met Gly Ala Ile Phe Thr Leu Ala Ala Leu
                 95                 100                 105
Lys Glu Ser Leu Ser Thr Cys Ile Pro Ala Ile Val Cys Leu Gly
                110                 115                 120
Phe Leu Leu Leu Leu Asn Val Gly Gln Leu Leu Ala Gln Thr Lys
                125                 130                 135
Lys Val Val Arg Pro Thr Arg Lys Lys Thr Leu Ser Thr Phe Lys
                140                 145                 150
Glu Ser Trp Lys


<210> 46
<211> 167
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 1726843


<400> 46
Met Ala Ser Pro Arg Thr Val Thr Ile Val Ala Leu Ser Val Ala
  1               5                  10                  15
Leu Gly Leu Phe Phe Val Phe Met Gly Thr Ile Lys Leu Thr Pro
                 20                  25                  30
Arg Leu Ser Lys Asp Ala Tyr Ser Glu Met Lys Arg Ala Tyr Lys
                 35                  40                  45
Ser Tyr Val Arg Ala Leu Pro Leu Leu Lys Lys Met Gly Ile Asn
                 50                  55                  60
Ser Ile Leu Leu Arg Lys Ser Ile Gly Ala Leu Glu Val Ala Cys
                 65                  70                  75
Gly Ile Val Met Thr Leu Val Pro Gly Arg Pro Lys Asp Val Ala
                 80                  85                  90
Asn Phe Phe Leu Leu Leu Leu Val Leu Ala Val Leu Phe Phe His
                 95                 100                 105
Gln Leu Val Gly Asp Pro Leu Lys Arg Tyr Ala His Ala Leu Val
                110                 115                 120
Phe Gly Ile Leu Leu Thr Cys Arg Leu Leu Ile Ala Arg Lys Pro
                125                 130                 135
Glu Asp Arg Ser Ser Glu Lys Lys Pro Leu Pro Gly Asn Ala Glu
                140                 145                 150
Glu Gln Pro Ser Leu Tyr Glu Lys Ala Pro Gln Gly Lys Val Lys
                155                 160                 165
Val Ser


<210> 47
<211> 545
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 1754506
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<400> 47
Met Ala Gly Ala Ile Ile Glu Asn Met Ser Thr Lys Lys Leu Cys
1 5 10 15
Ile Val Gly Gly Ile Leu Leu Val Phe Gln Ile Ile Ala Phe Leu
20 25 30
Val Gly Gly Leu Ile Ala Pro Gly Pro Thr Thr Ala Val Ser Tyr
35 40 45
Met Ser Val Lys Cys Val Asp Ala Arg Lys Asn His His Lys Thr
50 55 60
Lys Trp Phe Val Pro Trp Gly Pro Asn His Cys Asp Lys Ile Arg
65 70 75
Asp Ile Glu Glu Ala Ile Pro Arg Glu Ile Glu Ala Asn Asp Ile
80 85 90
Val Phe Ser Val His Ile Pro Leu Pro His Met Glu Met Ser Pro
95 100 105
Trp Phe Gln Phe Met Leu Phe Ile Leu Gln Leu Asp Ile Ala Phe
110 115 120
Lys Leu Asn Asn Gln Ile Arg Glu Asn Ala Glu Val Ser Met Asp
125 130 135
Val Ser Leu Ala Tyr Arg Asp Asp Ala Phe Ala Glu Trp Thr Glu
140 145 150
Met Ala His Glu Arg Val Pro Arg Lys Leu Lys Cys Thr Phe Thr
155 160 165
Ser Pro Lys Thr Pro Glu His Glu Gly Arg Tyr Tyr Glu Cys Asp
170 175 180
Val Leu Pro Phe Met Glu Ile Gly Ser Val Ala His Lys Phe Tyr
185 190 195
Leu Leu Asn Ile Arg Leu Pro Val Asn Glu Lys Lys Lys Ile Asn
200 205 210
Val Gly Ile Gly Glu Ile Lys Asp Ile Arg Leu Val Gly Ile His
215 220 225
Gln Asn Gly Gly Phe Thr Lys Val Trp Phe Ala Met Lys Thr Phe
230 235 240
Leu Thr Pro Ser Ile Phe Ile Ile Met Val Trp Tyr Trp Arg Arg
245 250 255
Ile Thr Met Met Ser Arg Pro Pro Val Leu Leu Glu Lys Val Ile
260 265 270
Phe Ala Leu Gly Ile Ser Met Thr Phe Ile Asn Ile Pro Val Glu
275 280 285
Trp Phe Ser Ile Gly Phe Asp Trp Thr Trp Met Leu Leu Phe Gly
290 295 300
Asp Ile Arg Gln Gly Ile Phe Tyr Ala Met Leu Leu Ser Phe Trp
305 310 315
Ile Ile Phe Cys Gly Glu His Met Met Asp Gln His Glu Arg Asn
320 325 330
His Ile Ala Gly Tyr Trp Lys Gln Val Gly Pro Ile Ala Val Gly
335 340 345
Ser Phe Cys Leu Phe Ile Phe Asp Met Cys Glu Arg Gly Val Gln
350 355 360
Leu Thr Asn Pro Phe Tyr Ser Ile Trp Thr Thr Asp Ile Gly Thr
365 370 375
Glu Leu Ala Met Ala Phe Ile Ile Val Ala Gly Ile Cys Leu Cys
380 385 390
Leu Tyr Phe Leu Phe Leu Cys Phe Met Val Phe Gln Val Phe Arg
395 400 405
Asn Ile Ser Gly Lys Gln Ser Ser Leu Pro Ala Met Ser Lys Val

```
                    410                     415                     420
Arg Arg Leu His Tyr Glu Gly Leu Ile Phe Arg Phe Lys Phe Leu
                    425                     430                     435
Met Leu Ile Thr Leu Ala Cys Ala Ala Met Thr Val Ile Phe Phe
                    440                     445                     450
Ile Val Ser Gln Val Thr Glu Gly His Trp Lys Trp Gly Gly Val
                    455                     460                     465
Thr Val Gln Val Asn Ser Ala Phe Phe Thr Gly Ile Tyr Gly Met
                    470                     475                     480
Trp Asn Leu Tyr Val Phe Ala Leu Met Phe Leu Tyr Ala Pro Ser
                    485                     490                     495
His Lys Asn Tyr Gly Glu Asp Gln Ser Asn Gly Met Gln Leu Pro
                    500                     505                     510
Cys Lys Ser Arg Glu Asp Cys Ala Leu Phe Val Ser Glu Leu Tyr
                    515                     520                     525
Gln Glu Leu Phe Ser Ala Ser Lys Tyr Ser Phe Ile Asn Asp Asn
                    530                     535                     540
Ala Ala Ser Gly Ile
                    545


<210> 48
<211> 570
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 1831378


<400> 48
Met Gly Phe Leu Gln Leu Leu Val Val Ala Val Leu Ala Ser Glu
  1                   5                  10                  15
His Arg Val Ala Gly Ala Ala Glu Val Phe Gly Asn Ser Ser Glu
                     20                  25                  30
Gly Leu Ile Glu Phe Ser Val Gly Lys Phe Arg Tyr Phe Glu Leu
                     35                  40                  45
Asn Arg Pro Phe Pro Glu Glu Ala Ile Leu His Asp Ile Ser Ser
                     50                  55                  60
Asn Val Thr Phe Leu Ile Phe Gln Ile His Ser Gln Tyr Gln Asn
                     65                  70                  75
Thr Thr Val Ser Phe Ser Pro Thr Leu Leu Ser Asn Ser Ser Glu
                     80                  85                  90
Thr Gly Thr Ala Ser Gly Leu Val Phe Ile Leu Arg Pro Glu Gln
                     95                 100                 105
Ser Thr Cys Thr Trp Tyr Leu Gly Thr Ser Gly Ile Gln Pro Val
                    110                 115                 120
Gln Asn Met Ala Ile Leu Leu Ser Tyr Ser Glu Arg Asp Pro Val
                    125                 130                 135
Pro Gly Gly Cys Asn Leu Glu Phe Asp Leu Asp Ile Asp Pro Asn
                    140                 145                 150
Ile Tyr Leu Glu Tyr Asn Phe Phe Glu Thr Thr Ile Lys Phe Ala
                    155                 160                 165
Pro Ala Asn Leu Gly Tyr Ala Arg Gly Val Asp Pro Pro Pro Cys
                    170                 175                 180
Asp Ala Gly Thr Asp Gln Asp Ser Arg Trp Arg Leu Gln Tyr Asp
```

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                    185                 190                 195
Val Tyr Gln Tyr Phe Leu Pro Glu Asn Asp Leu Thr Glu Glu Met
                    200                 205                 210
Leu Leu Lys His Leu Gln Arg Met Val Ser Val Pro Gln Val Lys
                    215                 220                 225
Ala Ser Ala Leu Lys Val Val Thr Leu Thr Ala Asn Asp Lys Thr
                    230                 235                 240
Ser Val Ser Phe Ser Ser Leu Pro Gly Gln Gly Val Ile Tyr Asn
                    245                 250                 255
Val Ile Val Trp Asp Pro Phe Leu Asn Thr Ser Ala Ala Tyr Ile
                    260                 265                 270
Pro Ala His Thr Tyr Ala Cys Ser Phe Glu Ala Gly Glu Gly Ser
                    275                 280                 285
Cys Ala Ser Leu Gly Arg Val Ser Ser Lys Val Phe Phe Thr Leu
                    290                 295                 300
Phe Ala Leu Leu Gly Phe Phe Ile Cys Phe Phe Gly His Arg Phe
                    305                 310                 315
Trp Lys Thr Glu Leu Phe Phe Ile Gly Phe Ile Ile Met Gly Phe
                    320                 325                 330
Phe Phe Tyr Ile Leu Ile Thr Arg Leu Thr Pro Ile Lys Tyr Asp
                    335                 340                 345
Val Asn Leu Ile Leu Thr Ala Val Thr Gly Ser Val Gly Gly Met
                    350                 355                 360
Phe Leu Val Ala Val Trp Trp Arg Phe Gly Ile Leu Ser Ile Cys
                    365                 370                 375
Met Leu Cys Val Gly Leu Val Leu Gly Phe Leu Ile Ser Ser Val
                    380                 385                 390
Thr Phe Phe Thr Pro Leu Gly Asn Leu Lys Ile Phe His Asp Asp
                    395                 400                 405
Gly Val Phe Trp Val Thr Phe Ser Cys Ile Ala Ile Leu Ile Pro
                    410                 415                 420
Val Val Phe Met Gly Cys Leu Arg Ile Leu Asn Ile Leu Thr Cys
                    425                 430                 435
Gly Val Ile Gly Ser Tyr Ser Val Val Leu Ala Ile Asp Ser Tyr
                    440                 445                 450
Trp Ser Thr Ser Leu Ser Tyr Ile Thr Leu Asn Val Leu Lys Arg
                    455                 460                 465
Ala Leu Asn Lys Asp Phe His Arg Ala Phe Thr Asn Val Pro Phe
                    470                 475                 480
Gln Thr Asn Asp Phe Ile Ile Leu Ala Val Trp Gly Met Leu Ala
                    485                 490                 495
Val Ser Gly Ile Thr Leu Gln Ile Arg Arg Glu Arg Gly Arg Pro
                    500                 505                 510
Phe Phe Pro Pro His Pro Tyr Lys Leu Trp Lys Gln Glu Arg Glu
                    515                 520                 525
Arg Arg Val Thr Asn Ile Leu Asp Pro Ser Tyr His Ile Pro Pro
                    530                 535                 540
Leu Arg Glu Arg Leu Tyr Gly Arg Leu Thr Gln Ile Lys Gly Leu
                    545                 550                 555
Phe Gln Lys Glu Gln Pro Ala Gly Glu Arg Thr Pro Leu Leu Leu
                    560                 565                 570
```

<210> 49
<211> 127
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 1864943

<400> 49
Met Arg Arg Arg Phe Trp Gly Val Phe Asn Cys Leu Cys Ala Gly
1 5 10 15
Ala Phe Gly Ala Leu Ala Ala Ala Ser Ala Lys Leu Ala Phe Gly
20 25 30
Ser Glu Val Ser Met Gly Leu Cys Val Leu Gly Ile Ile Val Met
35 40 45
Ala Ser Thr Asn Ser Leu Met Trp Thr Phe Phe Ser Arg Gly Leu
50 55 60
Ser Phe Ser Met Ser Ser Ala Ile Ala Ser Val Thr Val Thr Phe
65 70 75
Ser Asn Ile Leu Ser Ser Ala Phe Leu Gly Tyr Val Leu Tyr Gly
80 85 90
Glu Cys Gln Glu Val Leu Trp Trp Gly Gly Val Phe Leu Ile Leu
95 100 105
Cys Gly Leu Thr Leu Ile His Arg Lys Leu Pro Pro Thr Trp Lys
110 115 120
Pro Leu Pro His Lys Gln Gln
125

<210> 50
<211> 152
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 1911316

<400> 50
Met Asp Asn Val Gln Pro Lys Ile Lys His Arg Pro Phe Cys Phe
1 5 10 15
Ser Val Lys Gly His Val Lys Met Leu Arg Leu Ala Leu Thr Val
20 25 30
Thr Ser Met Thr Phe Phe Ile Ile Ala Gln Ala Pro Glu Pro Tyr
35 40 45
Ile Val Ile Thr Gly Phe Glu Val Thr Val Ile Leu Phe Phe Ile
50 55 60
Leu Leu Tyr Val Leu Arg Leu Asp Arg Leu Met Lys Trp Leu Phe
65 70 75
Trp Pro Leu Leu Asp Ile Ile Asn Ser Leu Val Thr Thr Val Phe
80 85 90
Met Leu Ile Val Ser Val Leu Ala Leu Ile Pro Glu Thr Thr Thr
95 100 105
Leu Thr Val Gly Gly Gly Val Phe Ala Leu Val Thr Ala Val Cys
110 115 120
Cys Leu Ala Asp Gly Ala Leu Ile Tyr Arg Lys Leu Leu Phe Asn
125 130 135
Pro Ser Gly Pro Tyr Gln Lys Lys Pro Val His Glu Lys Lys Glu
140 145 150
Val Leu

<210> 51
<211> 777
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 1943120

<400> 51
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Met Thr Phe Tyr Pro Phe Val Ala Ser Ser Ser Thr Arg Arg Val
  1               5                  10                  15
Asp Asn Ser Asn Thr Arg Leu Ala Val Gln Ile Glu Arg Asp Pro
                 20                  25                  30
Gly Asn Asp Asp Asn Asn Leu Asn Ser Ile Phe Tyr Glu His Leu
                 35                  40                  45
Thr Arg Thr Leu Leu Glu Ser Leu Cys Gly Asp Leu Val Leu Gly
                 50                  55                  60
Arg Trp Gly Asn Tyr Ser Ser Gly Asp Cys Phe Ile Leu Ala Ser
                 65                  70                  75
Asp Asp Leu Asn Ala Phe Val His Leu Ile Glu Ile Gly Asn Gly
                 80                  85                  90
Leu Val Thr Phe Gln Leu Arg Gly Leu Glu Phe Arg Gly Thr Tyr
                 95                 100                 105
Cys Gln Gln Arg Glu Val Glu Ala Ile Met Glu Gly Asp Glu Glu
                110                 115                 120
Asp Arg Gly Cys Cys Cys Cys Lys Pro Gly His Leu Pro His Leu
                125                 130                 135
Leu Ser Arg Asn Ala Ala Phe His Leu Arg Trp Leu Thr Trp Glu
                140                 145                 150
Ile Thr Gln Thr Gln Tyr Ile Leu Glu Gly Tyr Ser Ile Leu Asp
                155                 160                 165
Asn Asn Ala Ala Thr Met Leu Gln Val Phe Asp Leu Arg Arg Ile
                170                 175                 180
Leu Ile Arg Tyr Tyr Ile Lys Ser Ile Ile Tyr Tyr Met Val Thr
                185                 190                 195
Ser Pro Lys Leu Leu Ser Trp Ile Lys Asn Glu Ser Leu Leu Lys
                200                 205                 210
Ser Leu Gln Pro Phe Ala Lys Trp His Tyr Ile Glu Arg Asp Leu
                215                 220                 225
Ala Met Phe Asn Ile Asn Ile Asp Asp Asp Tyr Val Pro Cys Leu
                230                 235                 240
Gln Gly Ile Thr Arg Ala Ser Phe Cys Asn Val Tyr Leu Glu Trp
                245                 250                 255
Ile Gln His Cys Ala Arg Lys Arg Gln Glu Pro Ser Thr Thr Leu
                260                 265                 270
Asp Ser Asp Glu Asp Ser Pro Leu Val Thr Leu Ser Phe Ala Leu
                275                 280                 285
Cys Thr Leu Gly Arg Arg Ala Leu Gly Thr Ala Ala His Asn Met
                290                 295                 300
Ala Ile Ser Leu Asp Ser Phe Leu Tyr Gly Leu His Val Leu Phe
                305                 310                 315
Lys Gly Asp Phe Arg Ile Thr Ala Arg Asp Glu Trp Val Phe Ala
                320                 325                 330
Asp Met Asp Leu Leu His Lys Val Val Ala Pro Ala Ile Arg Met
```

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                335                     340                     345
Ser Leu Lys Leu His Gln Asp Gln Phe Thr Cys Pro Asp Glu Tyr
                350                     355                     360
Glu Asp Pro Ala Val Leu Tyr Glu Ala Ile Gln Ser Phe Glu Lys
                365                     370                     375
Lys Val Val Ile Cys His Glu Gly Asp Pro Ala Trp Arg Gly Ala
                380                     385                     390
Val Leu Ser Asn Lys Glu Glu Leu Leu Thr Leu Arg His Val Val
                395                     400                     405
Asp Glu Gly Ala Asp Glu Tyr Lys Val Ile Met Leu His Arg Ser
                410                     415                     420
Phe Leu Ser Phe Lys Val Ile Lys Val Asn Lys Glu Cys Val Arg
                425                     430                     435
Gly Leu Trp Ala Gly Gln Gln Gln Glu Leu Ile Phe Leu Arg Asn
                440                     445                     450
Arg Asn Pro Glu Arg Gly Ser Ile Gln Asn Asn Lys Gln Val Leu
                455                     460                     465
Arg Asn Leu Ile Asn Ser Ser Cys Asp Gln Pro Leu Gly Tyr Pro
                470                     475                     480
Met Tyr Val Ser Pro Leu Thr Thr Ser Tyr Leu Gly Thr His Arg
                485                     490                     495
Gln Leu Lys Asn Ile Trp Gly Gly Pro Ile Thr Leu Asp Arg Ile
                500                     505                     510
Arg Thr Trp Phe Trp Thr Lys Trp Val Arg Met Arg Lys Asp Cys
                515                     520                     525
Asn Ala Arg Gln His Ser Gly Gly Asn Ile Glu Asp Val Asp Gly
                530                     535                     540
Gly Gly Ala Pro Thr Thr Gly Gly Asn Asn Ala Pro Asn Gly Gly
                545                     550                     555
Ser Gln Glu Ser Ser Ala Glu Gln Pro Arg Lys Gly Gly Ala Gln
                560                     565                     570
His Gly Val Ser Ser Cys Glu Gly Thr Gln Arg Thr Gly Arg Arg
                575                     580                     585
Lys Gly Arg Ser Gln Ser Val Gln Ala His Ser Ala Leu Ser Gln
                590                     595                     600
Arg Pro Pro Met Leu Ser Ser Ser Gly Pro Ile Leu Glu Ser Arg
                605                     610                     615
Gln Thr Phe Leu Gln Thr Ser Thr Ser Val His Glu Leu Ala Gln
                620                     625                     630
Arg Leu Ser Gly Ser Arg Leu Ser Leu His Ala Ser Ala Thr Ser
                635                     640                     645
Leu His Ser Gln Pro Pro Pro Val Thr Thr Thr Gly His Leu Ser
                650                     655                     660
Val Arg Glu Arg Ala Glu Ala Leu Ile Arg Ser Ser Leu Gly Ser
                665                     670                     675
Ser Thr Ser Ser Thr Leu Ser Phe Leu Phe Gly Lys Arg Ser Phe
                680                     685                     690
Ser Ser Ala Leu Val Ile Ser Gly Leu Ser Ala Ala Glu Gly Gly
                695                     700                     705
Asn Thr Ser Asp Thr Gln Ser Ser Ser Ser Val Asn Ile Val Met
                710                     715                     720
Gly Pro Ser Ala Arg Ala Ala Ser Gln Ala Thr Arg Val Arg Gly
                725                     730                     735
Trp Ala Gly Leu Thr Arg Thr Gly Trp Asp Gly Gly Thr Gly Ser
                740                     745                     750
Trp Pro Glu Arg Gly Thr Cys Leu Ala Phe Pro Pro Phe Cys Leu
                755                     760                     765
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Gln Asn Pro Ile Pro Phe Ser Met Gly Leu Pro Glu
                770                 775


<210> 52
<211> 108
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2314236


<400> 52
Met Phe Lys His Glu Leu Glu Glu Leu Arg Thr Thr Ile Met Tyr
  1               5                  10                  15
Arg Asp Ser His Ser Val Leu Ala Leu Asn Trp Lys Val Val Ala
                 20                  25                  30
Thr Leu Lys Tyr Phe Leu Leu Tyr Val Ile Ile Leu Tyr Asn Leu
                 35                  40                  45
Glu Arg Asp Asn Gly His Ser Asn Tyr Glu Asn Tyr Glu Leu Gly
                 50                  55                  60
Asp Lys Ser Leu Asn Leu Leu Leu Phe Tyr Asn Ser Met Tyr Lys
                 65                  70                  75
Leu Val Phe Pro Tyr Ile Phe Thr Phe Ser Ser Phe Leu Ile Ser
                 80                  85                  90

Ser Tyr Thr Ser Ile Leu Tyr Lys Met Phe Tyr Ile Gln Arg Thr
                 95                 100                 105
Val Lys Ser


<210> 53
<211> 66
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2479409


<400> 53
Met Asn Leu Ser Lys Lys Ser Ile Leu Leu Thr Gln Val Ile Lys
  1               5                  10                  15
Phe Val Asp Ile Arg Leu Phe Ile Met Val Pro Ser Tyr Pro Phe
                 20                  25                  30
Asn Val Phe Arg Ser Cys Val Asp Asn Phe Leu Phe Ile Met Ile
                 35                  40                  45
Leu Val Ile Ser Val Leu Thr Phe Leu Ile Arg Leu Gly Arg Gly
                 50                  55                  60
Leu Ser Val Leu Leu Ile
                 65


<210> 54
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<211> 540
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2683149


<400> 54
Met Met Gly Ser Pro Val Ser His Leu Leu Ala Gly Phe Cys Val
  1               5                  10                  15
Trp Val Val Leu Gly Trp Val Gly Gly Ser Val Pro Asn Leu Gly
                 20                  25                  30
Pro Ala Glu Gln Glu Gln Asn His Tyr Leu Ala Gln Leu Phe Gly
                 35                  40                  45
Leu Tyr Gly Glu Asn Gly Thr Leu Thr Ala Gly Gly Leu Ala Arg
                 50                  55                  60
Leu Leu His Ser Leu Gly Leu Gly Arg Val Gln Gly Leu Arg Leu
                 65                  70                  75
Gly Gln His Gly Pro Leu Thr Gly Arg Ala Ala Ser Pro Ala Ala
                 80                  85                  90
Asp Asn Ser Thr His Arg Pro Gln Asn Pro Glu Leu Ser Val Asp
                 95                 100                 105
Val Trp Ala Gly Met Pro Leu Gly Pro Ser Gly Trp Gly Asp Leu
                110                 115                 120
Glu Glu Ser Lys Ala Pro His Leu Pro Arg Gly Pro Ala Pro Ser
                125                 130                 135
Gly Leu Asp Leu Leu His Arg Leu Leu Leu Leu Asp His Ser Leu
                140                 145                 150
Ala Asp His Leu Asn Glu Asp Cys Leu Asn Gly Ser Gln Leu Leu
                155                 160                 165
Val Asn Phe Gly Leu Ser Pro Ala Ala Pro Leu Thr Pro Arg Gln
                170                 175                 180
Phe Ala Leu Leu Cys Pro Ala Leu Leu Tyr Gln Ile Asp Ser Arg
                185                 190                 195
Val Cys Ile Gly Ala Pro Ala Pro Ala Pro Pro Gly Asp Leu Leu
                200                 205                 210
Ser Ala Leu Leu Gln Ser Ala Leu Ala Val Leu Leu Leu Ser Leu
                215                 220                 225
Pro Ser Pro Leu Ser Leu Leu Leu Leu Arg Leu Leu Gly Pro Arg
                230                 235                 240
Leu Leu Arg Pro Leu Leu Gly Phe Leu Gly Ala Leu Ala Val Gly
                245                 250                 255
Thr Leu Cys Gly Asp Ala Leu Leu His Leu Leu Pro His Ala Gln
                260                 265                 270
Glu Gly Arg His Ala Gly Pro Gly Gly Leu Pro Glu Lys Asp Leu
                275                 280                 285
Gly Pro Gly Leu Ser Val Leu Gly Gly Leu Phe Leu Leu Phe Val
                290                 295                 300
Leu Glu Asn Met Leu Gly Leu Leu Arg His Arg Gly Leu Arg Pro
                305                 310                 315
Arg Cys Cys Arg Arg Lys Arg Arg Asn Leu Glu Thr Arg Asn Leu
                320                 325                 330
Asp Pro Glu Asn Gly Ser Gly Met Ala Leu Gln Pro Leu Gln Ala
                335                 340                 345
Ala Pro Glu Pro Gly Ala Gln Gly Gln Arg Glu Lys Asn Ser Gln
```

350 355 360
His Pro Pro Ala Leu Ala Pro Pro Gly His Gln Gly His Ser His
365 370 375
Gly His Gln Gly Gly Thr Asp Ile Thr Trp Met Val Leu Leu Gly
380 385 390
Asp Gly Leu His Asn Leu Thr Asp Gly Leu Ala Ile Gly Ala Ala
395 400 405
Phe Ser Asp Gly Phe Ser Ser Gly Leu Ser Thr Thr Leu Ala Val
410 415 420
Phe Cys His Glu Leu Pro His Glu Leu Gly Asp Phe Ala Met Leu
425 430 435
Leu Gln Ser Gly Leu Ser Phe Arg Arg Leu Leu Leu Leu Ser Leu
440 445 450
Val Ser Gly Ala Leu Gly Leu Gly Gly Ala Val Leu Gly Val Gly
455 460 465
Leu Ser Leu Gly Pro Val Pro Leu Thr Pro Trp Val Phe Gly Val
470 475 480
Thr Ala Gly Val Phe Leu Tyr Val Ala Leu Val Asp Met Leu Pro
485 490 495
Ala Leu Leu Arg Pro Pro Glu Pro Leu Pro Thr Pro His Val Leu
500 505 510
Leu Gln Gly Leu Gly Leu Leu Leu Gly Gly Gly Leu Met Leu Ala
515 520 525

Ile Thr Leu Leu Glu Glu Arg Leu Leu Pro Val Thr Thr Glu Gly
530 535 540

<210> 55
<211> 87
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2774051

<400> 55
Met Pro Phe Thr Leu Asp Asp Tyr Gly Ala Tyr Ser Ser Gln Lys
1 5 10 15
Gln Tyr Thr Cys Gln Phe Pro Ser Thr Ile Ala Ile His Ala Glu
20 25 30
Asp Lys Arg Pro Pro Gln Ser Arg Arg Gly Ile Val Leu Gly Pro
35 40 45
Ile Phe Leu Ile Val Leu Lys Ile Ile Ile Arg Trp Thr Val Phe
50 55 60
Cys Glu Asp Phe Leu Phe Pro Ser Ser Lys Lys Pro Cys Gly Lys
65 70 75
Asn Ser Leu Ile Thr Val Leu Ile Phe Phe Phe Phe
80 85

<210> 56
<211> 100
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2869038

<400> 56
Met Ile Met Ala Gln Lys Ile Gly Gly Leu Thr Trp Trp Ala Ile
1 5 10 15
Met Phe Ile Ile Leu Phe Glu Ile Thr Gly Thr Ser Ser Ser Phe
20 25 30
Leu Arg Ile Asn Ala Leu Pro His Phe Ser Met Asn Arg Cys Gly
35 40 45
Glu Ala Tyr Phe Pro Phe Ser Tyr Leu Tyr Thr Ser Leu Gln Lys
50 55 60
Gln Phe Leu Met Lys Val Ser Gly Ile Val Lys Asn Leu Arg Gly
65 70 75
Met Met Thr Gly Gly Val Trp Gly Phe Phe Leu Tyr Ser Phe Phe
80 85 90
Asn Glu Lys Ser Phe Lys Cys Ser Thr Gly
95 100

<210> 57
<211> 58
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2918334

<400> 57
Met Asp Leu Leu Tyr Glu Ile Leu Leu Ala Leu Tyr Tyr Asn Ile
1 5 10 15
Cys Tyr Asp Ile Pro Phe Ile Phe Phe Asn Leu Asn Met Met Phe
20 25 30
Tyr Ile Val Leu Asp Leu Arg Ile Val Phe Phe Arg Thr Ile Arg
35 40 45
Glu Tyr Leu Ser Pro Pro Ser Leu Ser Phe Tyr Ile Tyr
50 55

<210> 58
<211> 61
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2949916

<400> 58
Met Arg Arg Ile Ile Arg Leu Arg Leu Arg Phe Ser Asp Thr Phe

```
  1               5                   10                  15
Met Ala Ala Phe Leu Leu Cys Leu Gly Phe Val Leu Met Leu Phe
                20                  25                  30
Pro Ser Leu Leu Arg Asp Gly Gly Ser Ile Ser Ser Cys Arg Asn
                35                  40                  45
Ser Cys Ser Ser Pro Ser Ser Glu Glu Arg His Phe Ser Asn Leu
                50                  55                  60
Glu
```

```
<210> 59
<211> 50
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2989375

<400> 59
Met Cys Leu Thr Pro His Arg Asp Ser Met Cys Glu Asp Ser Pro
  1               5                   10                  15
Phe Thr His Gln Ile Ile Ser Met Ala Thr Ala Cys Ser Leu Leu
                20                  25                  30
Leu Glu Cys Phe Val Leu Ala Ala Ser Leu Leu Val Cys Val Trp
                35                  40                  45
Ser Glu Trp Arg Arg
                50
```

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<210> 60
<211> 310
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 3316764

<400> 60
Met Arg Arg Thr Ala Phe Ile Leu Gly Ser Gly Leu Leu Ser Phe
  1               5                   10                  15
Val Ala Phe Trp Asn Ser Val Thr Trp His Leu Gln Arg Phe Trp
                20                  25                  30
Gly Ala Ser Gly Tyr Phe Trp Gln Ala Gln Trp Glu Arg Leu Leu
                35                  40                  45
Thr Thr Phe Glu Gly Lys Glu Trp Ile Leu Phe Phe Ile Gly Ala
                50                  55                  60
Ile Gln Val Pro Cys Leu Phe Phe Trp Ser Phe Asn Gly Leu Leu
                65                  70                  75
Leu Val Val Asp Thr Thr Gly Lys Pro Asn Phe Ile Ser Arg Tyr
                80                  85                  90
Arg Ile Gln Val Gly Lys Asn Glu Pro Val Asp Pro Val Lys Leu
                95                  100                 105
```

Arg Gln Ser Ile Arg Thr Val Leu Phe Asn Gln Cys Met Ile Ser
110 115 120
Phe Pro Met Val Val Phe Leu Tyr Pro Phe Leu Lys Trp Trp Arg
125 130 135
Asp Pro Cys Arg Arg Glu Leu Pro Thr Phe His Trp Phe Leu Leu
140 145 150
Glu Leu Ala Ile Phe Thr Leu Ile Glu Glu Val Leu Phe Tyr Tyr
155 160 165
Ser His Arg Leu Leu His His Pro Thr Phe Tyr Lys Lys Ile His
170 175 180
Lys Lys His His Glu Trp Thr Ala Pro Ile Gly Val Ile Ser Leu
185 190 195
Tyr Ala His Pro Ile Glu His Ala Val Ser Asn Met Leu Pro Val
200 205 210
Ile Val Gly Pro Leu Val Met Gly Ser His Leu Ser Ser Ile Thr
215 220 225
Met Trp Phe Ser Leu Ala Leu Ile Ile Thr Thr Ile Ser His Cys
230 235 240
Gly Tyr His Leu Pro Phe Leu Pro Ser Pro Glu Phe His Asp Tyr
245 250 255
His His Leu Lys Phe Asn Gln Cys Tyr Gly Val Leu Gly Val Leu
260 265 270
Asp His Leu His Gly Thr Asp Thr Met Phe Lys Gln Thr Lys Ala
275 280 285
Tyr Glu Arg His Val Leu Leu Leu Gly Phe Thr Pro Leu Ser Glu
290 295 300
Ser Ile Pro Asp Ser Pro Lys Arg Met Glu
305 310

<210> 61
<211> 160
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 3359559

<400> 61
Met Ala Pro Ala Leu Trp Arg Ala Cys Asn Gly Leu Met Ala Ala
1 5 10 15
Phe Phe Ala Leu Ala Ala Leu Val Gln Val Asn Asp Pro Asp Ala
20 25 30
Glu Val Trp Val Val Val Tyr Thr Ile Pro Ala Val Leu Thr Leu
35 40 45
Leu Val Gly Leu Asn Pro Glu Val Thr Gly Asn Val Ile Trp Lys
50 55 60
Ser Ile Ser Ala Ile His Ile Leu Phe Cys Thr Val Trp Ala Val
65 70 75
Gly Leu Ala Ser Tyr Leu Leu His Arg Thr Gln Gln Asn Ile Leu
80 85 90
His Glu Glu Glu Gly Arg Glu Leu Ser Gly Leu Val Ile Ile Thr
95 100 105
Ala Trp Ile Ile Leu Cys His Ser Ser Ser Lys Asn Pro Val Gly
110 115 120

```
Gly Arg Ile Gln Leu Ala Ile Ala Ile Val Ile Thr Leu Phe Pro
                125                 130                 135
Phe Ile Ser Trp Val Tyr Ile Tyr Ile Asn Lys Glu Met Arg Ser
                140                 145                 150
Ser Trp Pro Thr His Cys Lys Thr Val Ile
                155                 160


<210> 62
<211> 35
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 4289208


<400> 62
Met Ala Val Val Asp Ala Gly Asn Asn Gly Lys Val Leu Asp Arg
  1               5                  10                  15
Val Cys Val Arg Ser Val Pro Ala Leu Phe Leu Ser Lys Cys Ile
                 20                  25                  30
Ser Leu Asp Met Glu
                 35


<210> 63
<211> 323
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2454013


<400> 63
Met Ala Ala Pro Lys Gly Ser Leu Trp Val Arg Thr Gln Leu Gly
  1               5                  10                  15
Leu Pro Pro Leu Leu Leu Leu Thr Met Ala Leu Ala Gly Gly Ser
                 20                  25                  30
Gly Thr Ala Ser Ala Glu Ala Phe Asp Ser Val Leu Gly Asp Thr
                 35                  40                  45
Ala Ser Cys His Arg Ala Cys Gln Leu Thr Tyr Pro Leu His Thr
                 50                  55                  60
Tyr Pro Lys Glu Glu Glu Leu Tyr Ala Cys Gln Arg Gly Cys Arg
                 65                  70                  75
Leu Phe Ser Ile Cys Gln Phe Val Asp Asp Gly Ile Asp Leu Asn
                 80                  85                  90
Arg Thr Lys Leu Glu Cys Glu Ser Ala Cys Thr Glu Ala Tyr Ser
                 95                 100                 105
Gln Ser Asp Glu Gln Tyr Ala Cys His Leu Gly Cys Gln Asn Gln
                110                 115                 120
Leu Pro Phe Ala Glu Leu Arg Gln Glu Gln Leu Met Ser Leu Met
                125                 130                 135
Pro Lys Met His Leu Leu Phe Pro Leu Thr Leu Val Arg Ser Phe
```

```
                140                 145                 150
Trp Ser Asp Met Met Asp Ser Ala Gln Ser Phe Ile Thr Ser Ser
                155                 160                 165
Trp Thr Phe Tyr Leu Gln Ala Asp Asp Gly Lys Ile Val Ile Phe
                170                 175                 180
Gln Ser Lys Pro Glu Ile Gln Tyr Ala Pro His Leu Glu Gln Glu
                185                 190                 195
Pro Thr Asn Leu Arg Glu Ser Ser Leu Ser Lys Met Ser Tyr Leu
                200                 205                 210
Gln Met Arg Asn Ser Gln Ala His Arg Asn Phe Leu Glu Asp Gly
                215                 220                 225
Glu Ser Asp Gly Phe Leu Arg Cys Leu Ser Leu Asn Ser Gly Trp
                230                 235                 240
Ile Leu Thr Thr Thr Leu Val Leu Ser Val Met Val Leu Leu Trp
                245                 250                 255
Ile Cys Cys Ala Thr Val Ala Thr Ala Val Glu Gln Tyr Val Pro
                260                 265                 270
Ser Glu Lys Leu Ser Ile Tyr Gly Asp Leu Glu Phe Met Asn Glu
                275                 280                 285
Gln Lys Leu Asn Arg Tyr Pro Ala Ser Ser Leu Val Val Val Arg
                290                 295                 300
Ser Lys Thr Glu Asp His Glu Glu Ala Gly Pro Leu Pro Thr Lys
                305                 310                 315
Val Asn Leu Ala His Ser Glu Ile
                320
```

<210> 64
<211> 129
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2454048

<400> 64

```
Met Ala Arg Gly Ser Leu Arg Arg Leu Leu Arg Leu Leu Val Leu
  1             5                   10                  15
Gly Leu Trp Leu Ala Leu Leu Arg Ser Val Ala Gly Glu Gln Ala
                20                  25                  30
Pro Gly Thr Ala Pro Cys Ser Arg Gly Ser Ser Trp Ser Ala Asp
                35                  40                  45
Leu Asp Lys Cys Met Asp Cys Ala Ser Cys Arg Ala Arg Pro His
                50                  55                  60
Ser Asp Phe Cys Leu Gly Cys Ala Ala Ala Pro Pro Ala Pro Phe
                65                  70                  75
Arg Leu Leu Trp Pro Ile Leu Gly Gly Ala Leu Ser Leu Thr Phe
                80                  85                  90
Val Leu Gly Leu Leu Ser Gly Phe Leu Val Trp Arg Arg Cys Arg
                95                  100                 105
Arg Arg Glu Lys Phe Thr Thr Pro Ile Glu Glu Thr Gly Gly Glu
                110                 115                 120
Gly Cys Pro Ala Val Ala Leu Ile Gln
                125
```

<210> 65
<211> 461
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2479282

<400> 65
Met Ala Pro Gln Ser Leu Pro Ser Ser Arg Met Ala Pro Leu Gly
1 5 10 15
Met Leu Leu Gly Leu Leu Met Ala Ala Cys Phe Thr Phe Cys Leu
20 25 30
Ser His Gln Asn Leu Lys Glu Phe Ala Leu Thr Asn Pro Glu Lys
35 40 45
Ser Ser Thr Lys Glu Thr Glu Arg Lys Glu Thr Lys Ala Glu Glu
50 55 60
Glu Leu Asp Ala Glu Val Leu Glu Val Phe His Pro Thr His Glu
65 70 75
Trp Gln Ala Leu Gln Pro Gly Gln Ala Val Pro Ala Gly Ser His
80 85 90
Val Arg Leu Asn Leu Gln Thr Gly Glu Arg Glu Ala Lys Leu Gln
95 100 105
Tyr Glu Asp Lys Phe Arg Asn Asn Leu Lys Gly Lys Arg Leu Asp
110 115 120
Ile Asn Thr Asn Thr Tyr Thr Ser Gln Asp Leu Lys Ser Ala Leu
125 130 135
Ala Lys Phe Lys Glu Gly Ala Glu Met Glu Ser Ser Lys Glu Asp
140 145 150
Lys Ala Arg Gln Ala Glu Val Lys Arg Leu Phe Arg Pro Ile Glu
155 160 165
Glu Leu Lys Lys Asp Phe Asp Glu Leu Asn Val Val Ile Glu Thr
170 175 180
Asp Met Gln Ile Met Val Arg Leu Ile Asn Lys Phe Asn Ser Ser
185 190 195
Ser Ser Ser Leu Glu Glu Lys Ile Ala Ala Leu Phe Asp Leu Glu
200 205 210
Tyr Tyr Val His Gln Met Asp Asn Ala Gln Asp Leu Leu Ser Phe
215 220 225
Gly Gly Leu Gln Val Val Ile Asn Gly Leu Asn Ser Thr Glu Pro
230 235 240
Leu Val Lys Glu Tyr Ala Ala Phe Val Leu Gly Ala Ala Phe Ser
245 250 255
Ser Asn Pro Lys Val Gln Val Glu Ala Ile Glu Gly Gly Ala Leu
260 265 270
Gln Lys Leu Leu Val Ile Leu Ala Thr Glu Gln Pro Leu Thr Ala
275 280 285
Lys Lys Lys Val Leu Phe Ala Leu Cys Ser Leu Leu Arg His Phe
290 295 300
Pro Tyr Ala Gln Arg Gln Phe Leu Lys Leu Gly Gly Leu Gln Val
305 310 315
Leu Arg Thr Leu Val Gln Glu Lys Gly Thr Glu Val Leu Ala Val
320 325 330
Arg Val Val Thr Leu Leu Tyr Asp Leu Val Thr Glu Lys Met Phe
335 340 345

Ala Glu Glu Glu Ala Glu Leu Thr Gln Glu Met Ser Pro Glu Lys
350 355 360
Leu Gln Gln Tyr Arg Gln Val His Leu Leu Pro Gly Leu Trp Glu
365 370 375
Gln Gly Trp Cys Glu Ile Thr Ala His Leu Leu Ala Leu Pro Glu
380 385 390
His Asp Ala Arg Glu Lys Val Leu Gln Thr Leu Gly Val Leu Leu
395 400 405
Thr Thr Cys Arg Asp Arg Tyr Arg Gln Asp Pro Gln Leu Gly Arg
410 415 420
Thr Leu Ala Ser Leu Gln Ala Glu Tyr Gln Val Leu Ala Ser Leu
425 430 435
Glu Leu Gln Asp Gly Glu Asp Glu Gly Tyr Phe Gln Glu Leu Leu
440 445 450
Gly Ser Val Asn Ser Leu Leu Lys Glu Leu Arg
455 460

<210> 66
<211> 264
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2483432

<400> 66
Met Arg Pro Leu Leu Gly Leu Leu Leu Val Phe Ala Gly Cys Thr
1 5 10 15
Phe Ala Leu Tyr Leu Leu Ser Thr Arg Leu Pro Arg Gly Arg Arg
20 25 30
Leu Gly Ser Thr Glu Glu Ala Gly Gly Arg Ser Leu Trp Phe Pro
35 40 45
Ser Asp Leu Ala Glu Leu Arg Glu Leu Ser Glu Val Leu Arg Glu
50 55 60
Tyr Arg Lys Glu His Gln Ala Tyr Val Phe Leu Leu Phe Cys Gly
65 70 75
Ala Tyr Leu Tyr Lys Gln Gly Phe Ala Ile Pro Gly Ser Ser Phe
80 85 90
Leu Asn Val Leu Ala Gly Ala Leu Phe Gly Pro Trp Leu Gly Leu
95 100 105
Leu Leu Cys Cys Val Leu Thr Ser Val Gly Ala Thr Cys Cys Tyr
110 115 120
Leu Leu Ser Ser Ile Phe Gly Lys Gln Leu Val Val Ser Tyr Phe
125 130 135
Pro Asp Lys Val Ala Leu Leu Gln Arg Lys Val Glu Glu Asn Arg
140 145 150
Asn Ser Leu Phe Phe Phe Leu Leu Phe Leu Arg Leu Phe Pro Met
155 160 165
Thr Pro Asn Trp Phe Leu Asn Leu Ser Ala Pro Ile Leu Asn Ile
170 175 180
Pro Ile Val Gln Phe Phe Phe Ser Val Leu Ile Gly Leu Ile Pro
185 190 195
Tyr Asn Phe Ile Cys Val Gln Thr Gly Ser Ile Leu Ser Thr Leu
200 205 210

Thr Ser Leu Asp Ala Leu Phe Ser Trp Asp Thr Val Phe Lys Leu
215 220 225
Leu Ala Ile Ala Met Val Ala Leu Ile Pro Gly Thr Leu Ile Lys
230 235 240
Lys Phe Ser Gln Lys His Leu Gln Leu Asn Glu Thr Ser Thr Ala
245 250 255
Asn His Ile His Ser Arg Lys Asp Thr
260

<210> 67
<211> 339
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2493824

<400> 67
Met Ala Ala Ala Cys Gly Pro Gly Ala Ala Gly Tyr Cys Leu Leu
1 5 10 15
Leu Gly Leu His Leu Phe Leu Leu Thr Ala Gly Pro Ala Leu Gly
20 25 30
Trp Asn Asp Pro Asp Arg Met Leu Leu Arg Asp Val Lys Ala Leu
35 40 45
Thr Leu His Tyr Asp Arg Tyr Thr Thr Ser Arg Arg Leu Asp Pro
50 55 60
Ile Pro Gln Leu Lys Cys Val Gly Gly Thr Ala Gly Cys Asp Ser
65 70 75
Tyr Thr Pro Lys Val Ile Gln Cys Gln Asn Lys Gly Trp Asp Gly
80 85 90
Tyr Asp Val Gln Trp Glu Cys Lys Thr Asp Leu Asp Ile Ala Tyr
95 100 105
Lys Phe Gly Lys Thr Val Val Ser Cys Glu Gly Tyr Glu Ser Ser
110 115 120
Glu Asp Gln Tyr Val Leu Arg Gly Ser Cys Gly Leu Glu Tyr Asn
125 130 135
Leu Asp Tyr Thr Glu Leu Gly Leu Gln Lys Leu Lys Glu Ser Gly
140 145 150
Lys Gln His Gly Phe Ala Ser Phe Ser Asp Tyr Tyr Tyr Lys Trp
155 160 165
Ser Ser Ala Asp Ser Cys Asn Met Ser Gly Leu Ile Thr Ile Val
170 175 180
Val Leu Leu Gly Ile Ala Phe Val Val Tyr Lys Leu Phe Leu Ser
185 190 195
Asp Gly Gln Tyr Ser Pro Pro Pro Tyr Ser Glu Tyr Pro Pro Phe
200 205 210
Ser His Arg Tyr Gln Arg Phe Thr Asn Ser Ala Gly Pro Pro Pro
215 220 225
Pro Gly Phe Lys Ser Glu Phe Thr Gly Pro Gln Asn Thr Gly His
230 235 240
Gly Ala Thr Ser Gly Phe Gly Ser Ala Phe Thr Gly Gln Gln Gly
245 250 255

```
Tyr Glu Asn Ser Gly Pro Gly Phe Trp Thr Gly Leu Gly Thr Gly
                260                 265                 270
Gly Ile Leu Gly Tyr Leu Phe Gly Ser Asn Arg Ala Ala Thr Pro
                275                 280                 285
Phe Ser Asp Ser Trp Tyr Tyr Pro Ser Tyr Pro Pro Ser Tyr Pro
                290                 295                 300
Gly Thr Trp Asn Arg Ala Tyr Ser Pro Leu His Gly Gly Ser Gly
                305                 310                 315
Ser Tyr Ser Val Cys Ser Asn Ser Asp Thr Lys Thr Arg Thr Ala
                320                 325                 330
Ser Gly Tyr Gly Gly Thr Arg Arg Arg
                335
```

<210> 68
<211> 397
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2555823

<400> 68

```
Met Val Arg Pro Gly Ala Arg Leu Cys Leu Gly Ser Val Gly Arg
  1             5                   10                  15
Gly Leu Cys Leu Val Leu Pro Leu Leu Cys Leu Gly Ala Gly Phe
                20                  25                  30
Leu Phe Leu Asn Thr Leu Phe Ile Gln Arg Gly Arg His Glu Thr
                35                  40                  45
Thr Trp Thr Ile Leu Arg Arg Phe Gly Tyr Ser Asp Ala Leu Glu
                50                  55                  60
Leu Thr Ala Asp Tyr Leu Ser Pro Leu Ile His Val Pro Pro Gly
                65                  70                  75
Cys Ser Thr Glu Leu Asn His Leu Gly Tyr Gln Phe Val Gln Arg
                80                  85                  90
Val Phe Glu Lys His Asp Gln Asp Arg Asp Gly Ala Leu Ser Pro
                95                  100                 105
Val Glu Leu Gln Ser Leu Phe Ser Val Phe Pro Ala Ala Pro Trp
                110                 115                 120
Gly Pro Glu Leu Pro Arg Thr Val Arg Thr Glu Ala Gly Arg Leu
                125                 130                 135
Pro Leu His Gly Tyr Leu Cys Gln Trp Thr Leu Val Thr Tyr Leu
                140                 145                 150
Asp Val Arg Ser Cys Leu Gly His Leu Gly Tyr Leu Gly Tyr Pro
                155                 160                 165
Thr Leu Cys Glu Gln Asp Gln Ala His Ala Ile Thr Val Thr Arg
                170                 175                 180
Glu Lys Arg Leu Asp Gln Glu Lys Gly Gln Thr Gln Arg Ser Val
                185                 190                 195
Leu Leu Cys Lys Val Val Gly Ala Arg Gly Val Gly Lys Ser Ala
                200                 205                 210
Phe Leu Gln Ala Phe Leu Gly Arg Gly Leu Gly His Gln Asp Thr
                215                 220                 225
Arg Glu Gln Pro Pro Gly Tyr Ala Ile Asp Thr Val Gln Val Asn
                230                 235                 240
```

```
Gly Gln Glu Lys Tyr Leu Ile Leu Cys Glu Val Gly Thr Asp Gly
                245                 250                 255
Leu Leu Ala Thr Ser Leu Asp Ala Thr Cys Asp Val Ala Cys Leu
                260                 265                 270
Met Phe Asp Gly Ser Asp Pro Lys Ser Phe Ala His Cys Ala Ser
                275                 280                 285
Val Tyr Lys His His Tyr Met Asp Gly Gln Thr Pro Cys Leu Phe
                290                 295                 300
Val Ser Ser Lys Ala Asp Leu Pro Glu Gly Val Ala Val Ser Gly
                305                 310                 315
Pro Ser Pro Ala Glu Phe Cys Arg Lys His Arg Leu Pro Ala Pro
                320                 325                 330
Val Pro Phe Ser Cys Ala Gly Pro Ala Glu Pro Ser Thr Thr Ile
                335                 340                 345
Phe Thr Gln Leu Ala Thr Met Ala Ala Phe Pro His Leu Val His
                350                 355                 360
Ala Glu Leu His Pro Ser Ser Phe Trp Leu Arg Gly Leu Leu Gly
                365                 370                 375
Val Val Gly Ala Ala Val Ala Ala Val Leu Ser Phe Ser Leu Tyr
                380                 385                 390
Arg Val Leu Val Lys Ser Gln
                395
```

<210> 69
<211> 301
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2598242

<400> 69

```
Met Glu Leu Ser Asp Val Thr Leu Ile Glu Gly Val Gly Asn Glu
  1               5                  10                  15
Val Met Val Val Ala Gly Val Val Val Leu Ile Leu Ala Leu Val
                 20                  25                  30
Leu Ala Trp Leu Ser Thr Tyr Val Ala Asp Ser Gly Ser Asn Gln
                 35                  40                  45
Leu Leu Gly Ala Ile Val Ser Ala Gly Asp Thr Ser Val Leu His
                 50                  55                  60
Leu Gly His Val Asp His Leu Val Ala Gly Gln Gly Asn Pro Glu
                 65                  70                  75
Pro Thr Glu Leu Pro His Pro Ser Glu Gly Asn Asp Glu Lys Ala
                 80                  85                  90
Glu Glu Ala Gly Glu Gly Arg Gly Asp Ser Thr Gly Glu Ala Gly
                 95                 100                 105
Ala Gly Gly Gly Val Glu Pro Ser Leu Glu His Leu Leu Asp Ile
                110                 115                 120
Gln Gly Leu Pro Lys Arg Gln Ala Gly Ala Gly Ser Ser Ser Pro
                125                 130                 135
Glu Ala Pro Leu Arg Ser Glu Asp Ser Thr Cys Leu Pro Pro Ser
                140                 145                 150
Pro Gly Leu Ile Thr Val Arg Leu Lys Phe Leu Asn Asp Thr Glu
                155                 160                 165
```

Glu Leu Ala Val Ala Arg Pro Glu Asp Thr Val Gly Ala Leu Lys
170 175 180
Ser Lys Tyr Phe Pro Gly Gln Glu Ser Gln Met Lys Leu Ile Tyr
185 190 195
Gln Gly Arg Leu Leu Gln Asp Pro Ala Arg Thr Leu Arg Ser Leu
200 205 210
Asn Ile Thr Asp Asn Cys Val Ile His Cys His Arg Ser Pro Pro
215 220 225
Gly Ser Ala Val Pro Gly Pro Ser Ala Ser Leu Ala Pro Ser Ala
230 235 240
Thr Glu Pro Pro Ser Leu Gly Val Asn Val Gly Ser Leu Met Val
245 250 255
Pro Val Phe Val Val Leu Leu Gly Val Val Trp Tyr Phe Arg Ile
260 265 270
Asn Tyr Arg Gln Phe Phe Thr Ala Pro Ala Thr Val Ser Leu Val
275 280 285
Gly Val Thr Val Phe Phe Ser Phe Leu Val Phe Gly Met Tyr Gly
290 295 300
Arg

<210> 70
<211> 217
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2634120

<400> 70
Met Val Glu Val Gln Leu Glu Ser Asp His Glu Tyr Pro Pro Gly
1 5 10 15
Leu Leu Val Ala Phe Ser Ala Cys Thr Thr Val Leu Val Ala Val
20 25 30
His Leu Phe Ala Leu Met Val Ser Thr Cys Leu Leu Pro His Ile
35 40 45
Glu Ala Val Ser Asn Ile His Asn Leu Asn Ser Val His Gln Ser
50 55 60
Pro His Gln Arg Leu His Arg Tyr Val Glu Leu Ala Trp Gly Phe
65 70 75
Ser Thr Ala Leu Gly Thr Phe Leu Phe Leu Ala Glu Val Val Leu
80 85 90
Val Gly Trp Val Lys Phe Val Pro Ile Gly Ala Pro Leu Asp Thr
95 100 105
Pro Thr Pro Met Val Pro Thr Ser Arg Val Pro Gly Thr Leu Ala
110 115 120
Pro Val Ala Thr Ser Leu Ser Pro Ala Ser Asn Leu Pro Arg Ser
125 130 135
Ser Ala Ser Ala Ala Pro Ser Gln Ala Glu Pro Ala Cys Pro Pro
140 145 150
Arg Gln Ala Cys Gly Gly Gly Gly Ala His Gly Pro Gly Trp Gln
155 160 165
Ala Ala Met Ala Ser Thr Ala Ile Met Val Pro Val Gly Leu Val
170 175 180
Phe Val Ala Phe Ala Leu His Phe Tyr Arg Ser Leu Val Ala His

185 190 195

Lys Thr Asp Arg Tyr Lys Gln Glu Leu Glu Glu Leu Asn Arg Leu
200 205 210
Gln Gly Glu Leu Gln Ala Val
215

<210> 71
<211> 143
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2765411

<400> 71
Met Phe Pro Val Leu Gly Trp Ile Leu Ile Ala Val Val Ile Ile
1 5 10 15
Ile Leu Leu Ile Phe Thr Ser Val Thr Arg Cys Leu Ser Pro Val
20 25 30
Ser Phe Leu Gln Leu Lys Phe Trp Lys Ile Tyr Leu Glu Gln Glu
35 40 45
Gln Gln Ile Leu Lys Ser Lys Ala Thr Glu His Ala Thr Glu Leu
50 55 60
Ala Lys Glu Asn Ile Lys Cys Phe Phe Glu Gly Ser His Pro Lys
65 70 75
Glu Tyr Asn Thr Pro Ser Met Lys Glu Trp Gln Gln Ile Ser Ser
80 85 90
Leu Tyr Thr Phe Asn Pro Lys Gly Gln Tyr Tyr Ser Met Leu His
95 100 105
Lys Tyr Val Asn Arg Lys Glu Lys Thr His Ser Ile Arg Ser Thr
110 115 120
Glu Gly Asp Thr Val Ile Pro Val Leu Gly Phe Val Asp Ser Ser
125 130 135
Gly Ile Asn Ser Thr Pro Glu Leu
140

<210> 72
<211> 186
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2769412

<400> 72
Met Ser Gly Ile Ser Gly Cys Pro Phe Phe Leu Trp Gly Leu Leu
1 5 10 15
Ala Leu Leu Gly Leu Ala Leu Val Ile Ser Leu Ile Phe Asn Ile
20 25 30

```
Ser His Tyr Val Glu Lys Gln Arg Gln Asp Lys Met Tyr Ser Tyr
                35                  40                  45
Ser Ser Asp His Thr Arg Val Asp Glu Tyr Tyr Ile Glu Asp Thr
                50                  55                  60
Pro Ile Tyr Gly Asn Leu Asp Asp Met Ile Ser Glu Pro Met Asp
                65                  70                  75
Glu Asn Cys Tyr Glu Gln Met Lys Ala Arg Pro Glu Lys Ser Val
                80                  85                  90
Asn Lys Met Gln Glu Ala Thr Pro Ser Ala Gln Ala Thr Asn Glu
                95                  100                 105
Thr Gln Met Cys Tyr Ala Ser Leu Asp His Ser Val Lys Gly Lys
                110                 115                 120
Arg Arg Lys Pro Arg Lys Gln Asn Thr His Phe Ser Asp Lys Asp
                125                 130                 135
Gly Asp Glu Gln Leu His Ala Ile Asp Ala Ser Val Ser Lys Thr
                140                 145                 150
Thr Leu Val Asp Ser Phe Ser Pro Glu Ser Gln Ala Val Glu Glu
                155                 160                 165
Asn Ile His Asp Asp Pro Ile Arg Leu Phe Gly Leu Ile Arg Ala
                170                 175                 180
Lys Arg Glu Pro Ile Asn
                185
```

<210> 73
<211> 364
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2842779

<400> 73

```
Met Pro Gly Cys Pro Cys Pro Gly Cys Gly Met Ala Gly Pro Arg
  1             5                   10                  15
Leu Leu Phe Leu Thr Ala Leu Ala Leu Glu Leu Leu Gly Arg Ala
                20                  25                  30
Gly Gly Ser Gln Pro Ala Leu Arg Ser Arg Gly Thr Ala Thr Ala
                35                  40                  45
Cys Arg Leu Asp Asn Lys Glu Ser Glu Ser Trp Gly Ala Leu Leu
                50                  55                  60
Ser Gly Glu Arg Leu Asp Thr Trp Ile Cys Ser Leu Leu Gly Ser
                65                  70                  75
Leu Met Val Gly Leu Ser Gly Val Phe Pro Leu Leu Val Ile Pro
                80                  85                  90
Leu Glu Met Gly Thr Met Leu Arg Ser Glu Ala Gly Ala Trp Arg
                95                  100                 105
Leu Lys Gln Leu Leu Ser Phe Ala Leu Gly Gly Leu Leu Gly Asn
                110                 115                 120
Val Phe Leu His Leu Leu Pro Glu Ala Trp Ala Tyr Thr Cys Ser
                125                 130                 135
Ala Ser Pro Gly Gly Glu Gly Gln Ser Leu Gln Gln Gln Gln Gln
                140                 145                 150
Leu Gly Leu Trp Val Ile Ala Gly Ile Leu Thr Phe Leu Ala Leu
                155                 160                 165
```

Glu Lys Met Phe Leu Asp Ser Lys Glu Glu Gly Thr Ser Gln Ala
170 175 180
Pro Asn Lys Asp Pro Thr Ala Ala Ala Ala Ala Leu Asn Gly Gly
185 190 195
His Cys Leu Ala Gln Pro Ala Ala Glu Pro Gly Leu Gly Ala Val
200 205 210
Val Arg Ser Ile Lys Val Ser Gly Tyr Leu Asn Leu Leu Ala Asn
215 220 225
Thr Ile Asp Asn Phe Thr His Gly Leu Ala Val Ala Ala Ser Phe
230 235 240
Leu Val Ser Lys Lys Ile Gly Leu Leu Thr Thr Met Ala Ile Leu
245 250 255
Leu His Glu Ile Pro His Glu Val Gly Asp Phe Ala Ile Leu Leu
260 265 270
Arg Ala Gly Phe Asp Arg Trp Ser Ala Ala Lys Leu Gln Leu Ser
275 280 285
Thr Ala Leu Gly Gly Leu Leu Gly Ala Gly Phe Ala Ile Cys Thr
290 295 300
Gln Ser Pro Lys Gly Val Glu Glu Thr Ala Ala Trp Val Leu Pro
305 310 315
Phe Thr Ser Gly Gly Phe Leu Tyr Ile Ala Leu Val Asn Val Leu
320 325 330
Pro Asp Leu Leu Glu Glu Glu Asp Pro Trp Arg Ser Leu Gln Gln
335 340 345
Leu Leu Leu Leu Cys Ala Gly Ile Val Val Met Val Leu Phe Ser
350 355 360
Leu Phe Val Asp

<210> 74
<211> 605
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2966260

<400> 74
Met Gly Arg Leu Leu Arg Ala Ala Arg Leu Pro Pro Leu Leu Ser
1 5 10 15
Pro Leu Leu Leu Leu Leu Val Gly Gly Ala Phe Leu Gly Ala Cys
20 25 30
Val Ala Gly Ser Asp Glu Pro Gly Pro Glu Gly Leu Thr Ser Thr
35 40 45
Ser Leu Leu Asp Leu Leu Leu Pro Thr Gly Leu Glu Pro Leu Asp
50 55 60
Ser Glu Glu Pro Ser Glu Thr Met Gly Leu Gly Ala Gly Leu Gly
65 70 75
Ala Pro Gly Ser Gly Phe Pro Ser Glu Glu Asn Glu Glu Ser Arg
80 85 90

Ile Leu Gln Pro Pro Gln Tyr Phe Trp Glu Glu Glu Glu Glu Leu
95 100 105
Asn Asp Ser Ser Leu Asp Leu Gly Pro Thr Ala Asp Tyr Val Phe
110 115 120

Pro Asp Leu Thr Glu Lys Ala Gly Ser Ile Glu Asp Thr Ser Gln
125 130 135
Ala Gln Glu Leu Pro Asn Leu Pro Ser Pro Leu Pro Lys Met Asn
140 145 150
Leu Val Glu Pro Pro Trp His Met Pro Pro Arg Glu Glu Glu Glu
155 160 165
Glu Glu Glu Glu Glu Glu Glu Met Glu Lys Glu Glu Val Glu Lys
170 175 180
Gln Asp Val Glu Glu Glu Glu Glu Leu Leu Pro Val Asn Gly Ser
185 190 195
Gln Glu Glu Ala Lys Pro Gln Val Arg Asp Phe Ser Leu Thr Ser
200 205 210
Ser Ser Gln Thr Pro Gly Ala Thr Lys Ser Arg His Glu Asp Ser
215 220 225
Gly Asp Gln Ala Ser Ser Gly Val Glu Val Glu Ser Ser Met Gly
230 235 240
Pro Ser Leu Leu Leu Pro Ser Val Thr Pro Thr Ile Val Thr Pro
245 250 255
Gly Asp Gln Asp Ser Thr Ser Gln Glu Ala Glu Ala Thr Val Leu
260 265 270
Pro Ala Ala Gly Leu Gly Val Glu Phe Glu Ala Pro Gln Glu Ala
275 280 285
Ser Glu Glu Ala Thr Ala Gly Ala Ala Gly Leu Ser Gly Gln His
290 295 300
Glu Glu Val Pro Ala Leu Pro Ser Phe Pro Gln Thr Thr Ala Pro
305 310 315
Ser Gly Ala Glu His Pro Asp Glu Asp Pro Leu Gly Ser Arg Thr
320 325 330
Ser Ala Ser Ser Pro Leu Ala Pro Gly Asp Met Glu Leu Thr Pro
335 340 345
Ser Ser Ala Thr Leu Gly Gln Glu Asp Leu Asn Gln Gln Leu Leu
350 355 360
Glu Gly Gln Ala Ala Glu Ala Gln Ser Arg Ile Pro Trp Asp Ser
365 370 375
Thr Gln Val Ile Cys Lys Asp Trp Ser Asn Leu Ala Gly Lys Asn
380 385 390
Tyr Ile Ile Leu Asn Met Thr Glu Asn Ile Asp Cys Glu Val Phe
395 400 405
Arg Gln His Arg Gly Pro Gln Leu Leu Ala Leu Val Glu Glu Val
410 415 420
Leu Pro Arg His Gly Ser Gly His His Gly Ala Trp His Ile Ser
425 430 435
Leu Ser Lys Pro Ser Glu Lys Glu Gln His Leu Leu Met Thr Leu
440 445 450
Val Gly Glu Gln Gly Val Val Pro Thr Gln Asp Val Leu Ser Met
455 460 465
Leu Gly Asp Ile Arg Arg Ser Leu Glu Glu Ile Gly Ile Gln Asn
470 475 480
Tyr Ser Thr Thr Ser Ser Cys Gln Ala Arg Ala Ser Gln Val Arg
485 490 495
Ser Asp Tyr Gly Thr Leu Phe Val Val Leu Val Val Ile Gly Ala
500 505 510
Ile Cys Ile Ile Ile Ile Ala Leu Gly Leu Leu Tyr Asn Cys Trp
515 520 525
Gln Arg Arg Leu Pro Lys Leu Lys His Val Ser His Gly Glu Glu
530 535 540
Leu Arg Phe Val Glu Asn Gly Cys His Asp Asn Pro Thr Leu Asp

```
                    545                      550                      555
Val Ala Ser Asp Ser Gln Ser Glu Met Gln Glu Lys His Pro Ser
                    560                      565                      570
Leu Asn Gly Gly Gly Ala Leu Asn Gly Pro Gly Ser Trp Gly Ala
                    575                      580                      585
Leu Met Gly Gly Lys Arg Asp Pro Glu Asp Ser Asp Val Phe Glu
                    590                      595                      600
Glu Asp Thr His Leu
                    605
```

<210> 75
<211> 97
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2993326

<400> 75

```
Met Thr Gly Arg Phe Lys Ala Cys Gln Val Ile Leu Gly Leu Leu
  1               5                  10                  15
Val Ala Ile Ser Leu Ala Ala Gly Thr Gly Gly Ala Ala Gly Ala
                 20                  25                  30
Ala Leu Val Ile Val Phe Ile Gly Ala Phe Leu Val Leu Leu Phe
                 35                  40                  45
Leu Gly Arg Leu Thr Thr Gly Gly Ser Met Ala Arg Glu Ser Leu
                 50                  55                  60
Val Ala Ala Asn Arg Val Cys Ile Ser Arg Thr Leu Ser Ser Ser
                 65                  70                  75
Val Val Ser Val Cys Ile Ser Gly Gly Lys Gly Ser Pro Arg Leu
                 80                  85                  90
Pro Gly Gly Gly Arg Gly Pro
                 95
```

<210> 76
<211> 247
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 3001124

<400> 76

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Met Val Thr Leu Val Ser Asp Thr Ala Met Thr Pro Ile Ala Ser
  1               5                  10                  15
Val Asp Thr Ile Ala Val Cys Leu Phe Ala Gly Ala Trp Gly Gly
                 20                  25                  30
Ala Met Val Pro Met His Leu Leu Gly Arg Leu Glu Lys Pro Leu
                 35                  40                  45
Leu Leu Leu Cys Cys Ala Ser Phe Leu Leu Gly Leu Ala Leu Leu
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                    50                  55                  60
Gly Ile Lys Thr Asp Ile Thr Pro Val Ala Tyr Phe Phe Leu Thr
                    65                  70                  75
Leu Gly Gly Phe Phe Leu Phe Ala Tyr Leu Leu Val Arg Phe Leu
                    80                  85                  90
Glu Trp Gly Leu Arg Ser Gln Leu Gln Ser Met Gln Thr Glu Ser
                    95                 100                 105
Pro Gly Pro Ser Gly Asn Ala Arg Asp Asn Glu Ala Phe Glu Val
                   110                 115                 120
Pro Val Tyr Glu Glu Ala Val Val Gly Leu Glu Ser Gln Cys Arg
                   125                 130                 135
Pro Gln Glu Leu Asp Gln Pro Pro Pro Tyr Ser Thr Val Val Ile
                   140                 145                 150
Pro Pro Ala Pro Glu Glu Glu Gln Pro Ser His Pro Glu Gly Ser
                   155                 160                 165
Arg Arg Ala Lys Leu Glu Gln Arg Arg Met Ala Ser Glu Gly Ser
                   170                 175                 180
Met Ala Gln Glu Gly Ser Pro Gly Arg Ala Pro Ile Asn Leu Arg
                   185                 190                 195
Leu Arg Gly Pro Arg Ala Val Ser Thr Ala Pro Asp Leu Gln Ser
                   200                 205                 210
Leu Ala Ala Val Pro Thr Leu Glu Pro Leu Thr Pro Pro Pro Ala
                   215                 220                 225
Tyr Asp Val Cys Phe Gly His Pro Asp Asp Asp Ser Val Phe Tyr
                   230                 235                 240
Glu Asp Asn Trp Ala Pro Pro
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<210> 77
<211> 193
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 3120070

<400> 77

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Pro Leu Leu Leu Leu Ser Ala Ile Ala Phe Asp Ile Ile Ala Leu
                 20                  25                  30
Ala Gly Arg Gly Trp Leu Gln Ser Ser Asp His Gly Gln Thr Ser
                 35                  40                  45
Ser Leu Trp Trp Lys Cys Ser Gln Glu Gly Gly Gly Ser Gly Ser
                 50                  55                  60
Tyr Glu Glu Gly Cys Gln Ser Leu Met Glu Tyr Ala Trp Gly Arg
                 65                  70                  75
Ala Ala Ala Ala Met Leu Phe Cys Gly Phe Ile Ile Leu Val Ile
                 80                  85                  90
Cys Phe Ile Leu Ser Phe Phe Ala Leu Cys Gly Pro Gln Met Leu
                 95                 100                 105
Val Phe Leu Arg Val Ile Gly Gly Leu Leu Ala Leu Ala Ala Val
                110                 115                 120
Phe Gln Ile Ile Ser Leu Val Ile Tyr Pro Val Lys Tyr Thr Gln
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                125                     130                     135
Thr Phe Thr Leu His Ala Asn Pro Ala Val Thr Tyr Ile Tyr Asn
                140                     145                     150
Trp Ala Tyr Gly Phe Gly Trp Ala Ala Thr Ile Ile Leu Ile Gly
                155                     160                     165
Cys Ala Phe Phe Phe Cys Cys Leu Pro Asn Tyr Glu Asp Asp Leu
                170                     175                     180
Leu Gly Asn Ala Lys Pro Arg Tyr Phe Tyr Thr Ser Ala
                185                     190


<210> 78
<211> 128
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 3133035


<400> 78
Met Asn Met Lys Gln Lys Ser Val Tyr Gln Gln Thr Lys Ala Leu
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Leu Cys Lys Asn Phe Leu Lys Lys Trp Arg Met Lys Arg Glu Ser
                 20                  25                  30
Leu Leu Glu Trp Gly Leu Ser Ile Leu Leu Gly Leu Cys Ile Ala
                 35                  40                  45
Leu Phe Ser Ser Ser Met Arg Asn Val Gln Phe Pro Gly Met Ala
                 50                  55                  60
Pro Gln Asn Leu Gly Arg Val Asp Lys Phe Asn Ser Ser Ser Leu
                 65                  70                  75
Met Val Val Tyr Thr Pro Ile Ser Asn Leu Thr Gln Gln Ile Met
                 80                  85                  90
Asn Lys Thr Ala Leu Ala Pro Leu Leu Lys Gly Thr Ser Val Ile
                 95                 100                 105
Gly Ala Gln Ile Ile His Thr Trp Thr Lys Tyr Phe Trp Lys Ile
                110                 115                 120
Tyr Ile Cys Tyr Gly Asn His Leu
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<210> 79
<211> 115
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 3436879


<400> 79
Met Ala Val Ala Val Leu Leu Cys Gly Cys Ile Val Ala Thr Val
  1               5                  10                  15
Ser Phe Phe Trp Glu Glu Ser Leu Thr Gln His Val Ala Gly Leu
                 20                  25                  30
Leu Phe Leu Met Thr Gly Ile Phe Cys Thr Ile Ser Leu Cys Thr
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```
                35                   40                   45
Tyr Ala Ala Ser Ile Ser Tyr Asp Leu Asn Arg Leu Pro Lys Leu
                50                   55                   60
Ile Tyr Ser Leu Pro Ala Asp Val Glu His Gly Tyr Ser Trp Ser
                65                   70                   75
Ile Phe Cys Ala Trp Cys Ser Leu Gly Phe Ile Val Ala Ala Gly
                80                   85                   90
Gly Leu Cys Ile Ala Tyr Pro Phe Ile Ser Arg Thr Lys Ile Ala
                95                  100                  105
Gln Leu Lys Ser Gly Arg Asp Ser Thr Val
               110                  115
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<210> 80
<211> 1869
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 153831

<400> 80

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actctgccct cccctccctt taaccccctt ccagccggac gggaggcggg gcagggctga  180
gcatttgtga cacctacatt tccgtggctc ccttcttttc cccgaccccc tgtttatctc  240
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cacttggaag caggaggcgg ggttcagatc ttggccctac ccctcctgtg ttaaagtccg  360
cgagcctcag tttccctcac agtatttttt gcctcgcctt acccggtttt gaggatctgt  420
acgagaaaga gaaaggaagt ggacatttgt tgaattcctg catggccaaa taccacgcag  480
actgcttcat ccgccacgtt taatccttat tacttggtgt tctcagaact cccatttcat  540
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ctgcacagtg gagttcttct ccagagtctt cccttgtctg ggctctggct ggaactattc  660
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<210> 81
<211> 1044
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 350629

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<210> 82
<211> 3079
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 729171

<400> 82
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cggagtcccc agtgggcttc gggcatatga gtactacagg atgtgtatta aataaattgt 240
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<210> 83
<211> 1298
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte Clone No: 1273641

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<210> 84
<211> 2106
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 1427389

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aaaaaa 2106

<210> 85
<211> 899
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 1458357

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<210> 86
<211> 2000
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte Clone No: 2472514

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<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 3000380

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gcttgtgctg gtcttcttcc tcatgggcct ggtaggcttc atgatctgcc acgtgctcaa 240

gaagaagggc taccgctgcc gcacgtcgag gggctctgag cctgacgatg cccagcttca 300
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<211> 1581
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 182532

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aactgcccaa gtcacgattg aagcccagcc acccaaagtt tctgagggga aggatgttct 240
tctacttgtc cacaatttgc cccagaatct tgctggctac atttggtaca aagggcaaat 300
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gcctgcatac agtggaagag aaagagtata ttccaatgca tccctgctga tccagaatgt 420
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<210> 116
<211> 1566
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 239589

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aaaaaa 1566

<210> 117
<211> 1815
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte Clone No: 1671302

<400> 117

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cagatgccat cgtgaggaaa atgagccgga tgttctgtca ggctgcgaga gtggacctga  180
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<210> 118
<211> 1566
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2041858

<400> 118

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tcccagcaca ggcaaggagg aatccgagga taaggttctg gaggacaga agggcccaga  180
gagagtcctt agccaggatg gaggctgttg tgaacttgta ccaagaggtg atgaagcacg  240
cagatccccg gatccagggc taccctctga tggggtcccc cttgctaatg acctccattc  300
tcctgaccta cgtgtacttc gttctctcac ttgggcctcg catcatggct aatcggaagc  360
ccttccagct ccgtggcttc atgattgtct acaacttctc actggtggca ctctccctct  420
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atgtcataat gtacctgtac tacggattat ctgcctttgg ccctgtggca caaccctacc  780
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aaaaaa 1566

<210> 119
<211> 1055
<212> DNA
<213> Homo sapiens

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<221>
<222> 1032, 1037, 1042
<223> a or g or c or t, unknown, or other

<220>
<221> misc_feature
<223> Incyte Clone No: 2198863

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<210> 120
<211> 1956
<212> DNA
<213> Homo sapiens

<220>
<221>
<222> 1893, 1896, 1899, 1906, 1911, 1921, 1926, 1927, 1928, 1929, 1932, 1935, 1940, 1948, 1950, 1951, 1953
<223> a or g or c or t, unknown, or other

<220>
<221> misc_feature
<223> Incyte Clone No: 3250703

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naaaannnnt anttnagccn ctgttgtntn nanacc 1956

<210> 121
<211> 1737
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 350287

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<211> 789
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte Clone No: 1618171

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<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte Clone No: 2314236

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taaagatagg cataaatagt tgtccttaga cttattcata caaatatagt catttacttc 540

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<213> Homo sapiens

<220>
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<210> 133
<211> 1922
<212> DNA
<213> Homo sapiens

<220>
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aa 1922

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<213> Homo sapiens

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<222> 814
<223> a or g or c or t, unknown, or other

<220>
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<223> Incyte Clone No: 2774051

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gttcctttag gctagattaa gcagccattc attgttagag cctggagacc ttattcgaag 360
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cacctgtcag tttccatcaa ctatagcaat ccatgcagaa gacaagaggc cccctcaaag 540
caggaggggt attgttttag gtccaatttt tcttattgtt ctcaaaatca ttataaggtg 600
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<212> DNA
<213> Homo sapiens

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<223> Incyte Clone No: 2869038

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<211> 443
<212> DNA
<213> Homo sapiens

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gcgatcagaa tttctgagat tatttatgtg actatttttg gaaaagtttc ttttgataaa 180
acatggattt attatatgaa attcttcttg cactgtatta caatatatgc tatgatatcc 240
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<212> DNA
<213> Homo sapiens

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<211> 902
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<213> Homo sapiens

<220>
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<212> DNA
<213> Homo sapiens

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<211> 1252
<212> DNA
<213> Homo sapiens

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<223> Incyte Clone No: 3359559

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<212> DNA

<213> Homo sapiens

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<213> Homo sapiens

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<213> Homo sapiens

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<220>
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<223> Incyte Clone No: 2493824

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<211> 1790
<212> DNA
<213> Homo sapiens

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<223> Incyte Clone No: 2555823

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<211> 1979
<212> DNA
<213> Homo sapiens

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<223> Incyte Clone No: 2598242

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<211> 1810
<212> DNA
<213> Homo sapiens

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<223> Incyte Clone No: 2634120

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<212> DNA
<213> Homo sapiens

<220>
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<210> 151
<211> 891
<212> DNA
<213> Homo sapiens

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<221> misc_feature
<223> Incyte Clone No: 2769412

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<210> 152
<211> 2311
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte Clone No: 2842779

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<211> 2169
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2966260

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<210> 154
<211> 1480
<212> DNA
<213> Homo sapiens

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<210> 156
<211> 1983
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 3120070

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<210> 157
<211> 1835
<212> DNA
<213> Homo sapiens

<220>

<221> misc_feature
<223> Incyte Clone No: 3133035

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